Clinical Trial Protocol

EC-18 for Management of Chemotherapy-Induced Neutropenia in Patients with Advanced Breast Cancer Receiving Low Febrile Neutropenia Risk Chemotherapy: Dose-Escalation, Open-label, Multicentre Clinical Trial to Assess the Safety and Tolerability of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen

United States Protocol Number: EC-18-201
Protocol Amendment 3
Version No. 5.2 (11 June 2017)

CONFIDENTIAL

Confidentiality: All information contained in this protocol has been provided for the principal investigator, study staff, institutional review board and public health authorities and must not be disclosed to a third party without written consent of Enzychem Lifesciences Corporation.

PROTOCOL VERSION HISTORY

Description of Change	Protocol Section Affected by the Change	Rationale
• Follow-up period is extended from 14 days to 28 days	Protocol Summary Study Flow Chart Subjects' Participation Period (Section 8.2) Method of the Clinical Study (Section 8.4) Day 22 and Day 50 Visits (Section 9.2.5) Table 3 Physical Exam (Section 12.4.3) Vital Signs (Section 12.4.4) Electrocardiogram (Section 12.4.6) Clinical Laboratory Tests (Section 12.4.7)	Change requested by the Food and Drug Administration

PROTOCOL SUMMARY

Sponsor	Enzychem Lifesciences Corporation
Name of drugs used in the clinical study	EC-18 Soft-capsule
Main active ingredients	1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol
Protocol Number	EC-18-201
Clinical study title	EC-18 for Management of Chemotherapy-Induced Neutropenia in Patients with Advanced Breast Cancer Receiving Low Febrile Neutropenia Risk Chemotherapy: Dose-Escalation, Open-label, Multicentre Clinical Trial to Assess the Safety and Tolerability of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen
Study center and principle investigator	Study center: About 6 centers (In Korea: About 3 centers, Overseas (U.S.): About 3 centers) Principal Investigator: Professor Sung Bae Kim, Oncology Department, Asan Medical Center
Clinical study phase	Phase 1
Clinical Study Period	24 months from the date of approval by Ministry of Food and Drug Safety and Institutional Review Board
Study rationale	In the studies on the Mode of Action of EC-18 using animal models, orally administered EC-18 produced the reduction of frequency, severity and duration of the occurrence of chemotherapy-induced neutropenia. In the study using pseudomonas-infected animals, the EC-18-treated group showed longer overall survival as compared to control group. It was noted that the effective dose maintaining absolute neutrophil counts (ANCs) was observed with no or insignificant toxicity. In the pilot case-controlled study with 16 pancreatic cancer patients, the patients receiving EC-18 experienced lower incidence of infection and neutropenia as compared with the control group. This clinical trial implements “3+3” dose escalation design and once-daily administration to advanced breast cancer patients in 4 cohorts and aims at primarily determining of a maximum safe dose and possibly, observation of dose limiting toxicity (DLT).

Objectives	**Primary Objective:** The primary objective of this study is to demonstrate safety and significant recovery of grade 4 neutropenia when EC-18 is administered to patients with relapsing or metastatic breast cancer patients whose risk level for febrile neutropenia is low and who are receiving second line or higher chemotherapy (including endocrine therapy) that incorporates doxorubicin/cyclophosphamide. The first 15 days of daily absolute neutrophil count and the period to recover the absolute neutrophil count (ANC) to ≥1.5 x 10^9/L will be analyzed as primary endpoints. **Criteria of failure in, and discontinuation of, treatment:** Failure in EC-18 treatment is determined and discontinuation of EC-18 treatment is considered by the following method during the chemotherapy treatment period. 1. List and identify the properties of all serious infectious adverse events requiring systemic antibiotics or inpatient therapy; Subjects who have been identified as having these serious adverse events are considered treatment failures regardless of the treatment group. 2. Febrile episode (oral temperature >100.6 °F [38 °C]) with neutropenia (all grades): Subjects with febrile neutropenia are considered as secondary treatment failures. In the event of febrile neutropenia, rapid-onset granulocyte colony-stimulating factor rescue therapy may be performed according to the judgment of the investigator and standard of care. If the subject has received interventional treatment with a short-acting granulocyte stimulating factor (as recommended by the 2015 ASCO clinical practice guideline update) based on the investigator's judgment and standard of care, administration of study drug will be discontinued. 3. Clinical symptoms and clinically significant abnormal laboratory test results will be evaluated to compare severity, duration, and sequelae of all adverse events associated with EC-18. Subjects who have withdrawn due to the occurrence of an adverse event will be regarded as treatment failures regardless of the treatment group. **Secondary objective:** To determine the maximum tolerated dose (MTD) and confirm the safety of EC-18.
Target disease	Patients with advanced breast cancer who are receiving chemotherapy and whose risk level is low for febrile neutropenia.
Clinical study design	The primary and secondary objectives of this study are to assess the safety of doses and determine the doses to be used for evaluating the pharmacodynamic activity in patients with relapsed / metastatic breast cancer receiving specific dual chemotherapies. The dose of EC-18 will be escalated according to a typical 3 + 3 dose escalation design. Three subjects in each group will be administered the first oral dose (or escalated oral doses

<table>
<tr><td></td><td>corresponding to the cohorts in which they are assigned) 30 minutes after breakfast.

Since EC-18 has been shown to maintain high systemic exposure and low variability when taken orally with food, all subjects are instructed to take EC-18 after meals. The dose escalation phase has been planned based upon the clinical and non-clinical experience to date, and all 4 dose cohorts will be completed if no dose-limiting toxicities are experienced. The initial dose of this study was carefully reviewed by the sponsor, external experts, as well as by FDA's Division of Hematology Products. The basis for the initial dose is described in Section 4.5. The four doses planned are 500 mg, 1000 mg, 1500 mg, and 2000 mg. In the event of a DLT, 3 subjects will be added to the cohort. The primary objective of the study is to determine the safe and pharmacologically active dose to be administered in Part 2.

Safety and drug tolerance during the entire course of the study will be monitored through physical examination, electrocardiogram (12-lead ECG), vital signs, adverse events, and laboratory test results.</td></tr>
<tr><td>Number of subjects</td><td>A total of 12 subjects are planned initially for enrollment: 4 dosing cohorts (500 mg, 1000 mg, 1500 mg, and 2000 mg), each enrolling 3 subjects initially. If the first DLT occurs in any cohort, the cohort will be expanded by an additional 3 subjects who will receive the same dose. If applicable, this expansion would increase the number of subjects in a given cohort to 6. If the second DLT occurs in the expanded cohort, no more subjects will be added and dose escalation will be stopped. This dosing scheme based on DLTs is shown below.

<table>
<tr><th>Number of subjects developing DLT/total number of subjects in a cohort</th><th>Actions and plan of addition of subjects</th></tr>
<tr><td>0/3</td><td>Dose escalation</td></tr>
<tr><td>1/3</td><td>Addition of 3 subjects to the running cohort (expansion of the cohort)</td></tr>
<tr><td>≥2/3</td><td>Halt dose escalation</td></tr>
<tr><td>1/6</td><td>Dose escalation</td></tr>
<tr><td>≥2/3</td><td>Halt of dose escalation</td></tr>
</table></td></tr>
<tr><td>Study termination criteria</td><td>Subjects who participate in the study may stop their study participation due to adverse events, lack of effects, or for any other personal reasons. The Data and Safety Monitoring Committee (DSMC), Institutional Review Board, or regulatory authorities may recommend that the sponsor discontinue the study at any time regardless of reasons. The expected incidence rate of febrile neutropenia in subjects receiving a maximum dose of doxorubicin and cyclophosphamide is approximately 10%. If the incidence rate of febrile neutropenia is increased by up to 30% in subjects receiving EC-18, it will be considered a case of unacceptable failure rate and the cause for discontinuation of clinical study due to futility or adverse effects of the study drug.</td></tr>
</table>

Inclusion Criteria	1) Women ≥19 years of age 2) Subjects who have voluntarily signed the informed consent prior to the screening tests to participate in the study 3) Subjects who have been diagnosed as adenocarcinoma of the breast and relapsed after adjuvant or primary (neoadjuvant) chemotherapy, and thus through history have been confirmed to be candidates for chemotherapy of second line or higher (including hormonal therapy) combined with doxorubicin and cyclophosphamide to treat relapsed or metastatic disease. 4) Subjects with adequate organ function based on the following clinical laboratory values in the final examination performed within 14 days prior to dosing: • Neutrophil count (ANC): ≥1,500/mm^3 • Platelet count: ≥10.0×10^4/mm^3 • Hemoglobin: ≥9.0 g/dL • AST, ALT: ≤3.0 x ULN • Serum total bilirubin: ≤1.5 mg/dL • Serum creatinine: ≤1.5 mg/dL 5) Subjects with Eastern Cooperative Oncology Group (ECOG) performance score of 0-1. 6) For women of child bearing potential, subjects should have willingness to use acceptable contraceptive methods during the entire clinical study period. 7) Subjects who are capable of understanding the overall procedure of the clinical trial and are willing to participate in compliance with all test procedures.
Exclusion criteria	1) Subjects with active and inactive hepatitis, patients with HIV, or other uncontrolled infectious disease. 2) Subjects who received radiation therapy within 4 weeks of treatment assignment. 3) Subjects who have been diagnosed within 5 years with other types of cancer except for those who have been appropriately treated for superficial non-melanoma skin cancer or cervical intraepithelial neoplasia. 4) Subjects with a history of intolerance for granulocyte colony stimulating factor treatment

	5) Subjects who are expected to show hypersensitivity to the study drug or its ingredients 6) Subjects with a positive urine pregnancy test result prior to the screening visit or the first administration of the study drug 7) Subjects who took any other study drug used in a clinical trial within 30 days prior to the screening visit. 8) Clinically significant unstable medical abnormality; psychiatric disorder, chronic disease, alcohol or drug use disorder, or other significant biological, psychological, or social factor, which in the investigator's opinion, unfavorably affects the risk-benefit ratio of study participation is likely to interfere with satisfactory study completion or confound its outcome. 9) Subjects with unstable heart disease (Example: Congestive heart failure, arrhythmia, symptomatic coronary artery disease); Myocardial infarction within 6 months before initiation of the study. 10) Subjects with left ventricular ejection fraction (LVEF) < 50% at screening. 11) Significant neurological or psychiatric disorders including dementia or seizures. 12) Subjects with poorly controlled hypertriglyceridemia (>500mg/dL) with use of hypolipidemic agents. 13) Subjects with poorly controlled diabetes (fasting glucose> 150 mg / dL or HbA1c ≥ 8%). 14) Subjects who have received systemic chemotherapy with doxorubicin anticancer agent to treat metastatic or recurrent breast cancer 15) Subjects with Grade 2 or higher peripheral sensory neuropathy prior to the screening visit or first dosing of the study drug 16) Subjects who have undergone significant gastrectomy with intractable nausea and vomiting, chronic gastrointestinal disease, or clinically significant sequelae, which would interfere with proper absorption of the study drug 17) Subjects who were administered with systemic antibiotics within 14 days prior to administration of the study drug 18) Subjects who are currently receiving trastuzumab
Dosage and method of administering the study drug	Each capsule contains EC-18 500 mg. EC-18 is administered orally approximately 30 minutes after breakfast. Co-administration with meals may be substituted with a commercial formulation (such as SlimFast or Ensure). Orally administer up to a total of 500 (1 capsule) mg, 1000 mg, 1500 mg or 2000 mg (4 capsules) once daily

	Chemotherapy agents: Mild degree of risk for febrile neutropenia All subjects who will be screened for participation in this study should be recurrent or relapsed breast cancer patients and the confirmed risk for febrile neutropenia should be low. Subjects will provide informed consent before receiving study medication. Subjects whose risk for febrile neutropenia is low will consent to receive chemotherapy.
Administration period	Dose escalation group: 7 weeks (3 weeks of administration period and 4 weeks of safety follow-up investigation); Effectiveness of EC-18 is monitored for 3 weeks (1st cycle) and safety is monitored for 7 weeks by adding 4 weeks of follow-up observation period to the 1st cycle (3 weeks).
Efficacy Endpoints	**Primary efficacy endpoint** Duration of restoration to ANC $\geq 1.5 \times 10^9$/L within the first 15 days **Secondary efficacy endpoint** 1) Frequency of Grade 3-4 neutropenia (as defined by NCI CTCAE version 4.03) 2) Incidence rate of febrile neutropenia (as defined by NCI CTCAE version 4.03) 3) Time to reach ANC nadir and to recover to Grade 2 or lower neutropenia 4) Frequency of IV administration of antibiotics and hospitalization 5) Requirement for treatment intervention with rapid-acting granulocyte colony stimulating factor for subjects with febrile neutropenia who are at high risk for infection-associated complication or who have prognostic factors that predict poor clinical outcomes (as recommended by the 2015 ASCO clinical practice guideline update)
Safety Endpoints	1) All adverse events (AE), serious adverse events (SAE), and incidence rate of adverse events (AE, SAE) that resulted in discontinuation of administration. 2) Laboratory test (hematological test, blood chemistry test, coagulation test and urine test result analysis) -- absolute values and changes from the baseline 3) Vital Signs, Weight, 12-lead ECG -- absolute values and changes from the baseline

STUDY FLOW CHART

Assessment	Screening	Treatment Phase				
	Week -4 to -1	Week 1	Week 2	Week 3	Week 4	Week 8[j]
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 50
	Visit 1	Visit 2	Visit 3 (±2 days)	Visit 4 (±2 days)	Visit 5 (±2 days)	Visit 6 (±2 days)
Informed consent	X					
Randomization		X				
Inclusion/exclusion criteria	X	X				
Medical history	X					
ECG [a]	X	X[b]			X	X
LVEF	X					
Chest X-ray	X				(X)	X
Concomitant medications	X	X	X	X	X	X
Weight and height [c]	X	X[c]	X[c]	X[c]	X[c]	X[c]
Vital signs	X	X	X	X	X	X
Physical examination	X[d]	X[e]	X[e]	X[e]	X[e]	X[e]
ECOG performance status	X	X			X	X
CBC with differential [f]	X	daily			X	X
Serum chemistry	X	X[b]	X	X	X	X
Coagulation tests	X	X[b]	X	X	X	X
Urinalysis	X					X

Footnotes appear on the last page of this table.

Assessment	Screening	Treatment Phase				
	Week -4 to -1	Week 1	Week 2	Week 3	Week 4	Week 8[j]
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 50
	Visit 1	Visit 2	Visit 3 (±2 days)	Visit 4 (±2 days)	Visit 5 (±2 days)	Visit 6 (±2 days)
Urine pregnancy test	X	X[b]			X	X
Virus serology	X					
Reticulocyte count		X	X		X	X
EC-18[g]		Given orally once daily for the first 21 days				
Chemotherapy h		X[i]				
Adverse events	X	X	X	X	X	X
Admission		X[k]		X[k]		

CBC = whole blood count and differential blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group

a. Electrocardiogram (ECG) must be measured prior to drawing blood.
b. As for CBC, serum chemistry, coagulation test, urine pregnancy test, and ECG, if the test was performed within 1 week of randomization (Day 1 visit), it is not necessary to repeat the tests at Day 1 visit.
c. Height is measured only at screening visit.
d. A full physical examination involving the following body parts and systems: Overall appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, chest, lymph node, limb, nerve, skin, and musculoskeletal system.
e. Restricted/focused physical examination including the following parts of the body and systems: Overall appearance, cardiovascular, lungs, abdominal area, chest, lymph node, and areas / systems needed for AE evaluation.
f. CBC includes red blood cell count, hemoglobin, hematocrit, red blood cell count, white blood cell count, differential blood count (absolute and percentage) and platelet count. The CBC and differential blood counts are checked daily until Day 15 or until ANC ≥ 1.5 x 109 / L is restored during the first chemotherapy cycle.
g. The first dose (Day 1) is administered after the assessment at Day 1 visit in hospitals and randomization. All subsequent study drug administration is self-administered at home by the subjects themselves. The subjects should record the date and time of dosing, the status and time of vomiting, and the reasons for missed dose if applicable.

h. Doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2. Prior to the administration of chemotherapy agent, the cumulative dose of anthracycline and LVEF are checked to assess the risk of heart failure. Administration of chemotherapy agents may be postponed until the laboratory test values are restored, but the delay should not exceed a maximum of 3 weeks (21 days).
i. The first cycle (Day 1) of chemotherapy is administered after the assessment at Day 1 visit and randomization. At Day 1, adverse events should be evaluated during and after chemotherapy.
j. Final follow-up is performed at Day 50.
k. Procedures scheduled at Day 1-2 and Day 15-16 are carried out during hospitalization.

DEFINITIONS OF ABBREVIATIONS AND TERMS

Abbreviations	Definitions
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under The Plasma Concentration Versus Time Curve
C	Complement Factor
CBC	Complete Blood Count with differential count
CIN	(Chemotherapy-Induced Neutropenia)
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	MultiGated Acquisition
NCI	National Cancer Institute
PLAG	1-palmitoyl-2-linoleoyl-3-acetyl-rac-glyerol
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAR	Suspected Adverse Drug Reaction
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit Of Normal

Abbreviations	Definitions
WBC	White Blood Cell

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TITLE AND PHASE OF THE CLINICAL STUDY

Title: EC-18 for Management of Severe Chemotherapy-Induced Neutropenia in Patients with Advanced Breast Cancer Receiving Low Febrile Neutropenia Risk Chemotherapy: Dose-Escalation, Open-label, Multicentre Clinical Trial to Assess the Safety and Tolerability of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen

The name and address of the principal investigator and subinvestigators are listed in Form FDA 1572 (Module 5).

1. SPONSOR AND CONTRACT RESEARCH ORGANIZATION

1.1. Study Sponsor

Name of company	CEO	Business location	Telephone
Enzychem Lifesciences Corporation	Ki Young Sohn	15Th Floor, Trust Tower, 60, Mabang-ro, Seocho-gu, Seoul, Republic of Korea (Postal Code: 06775)	82-501-1084

1.2. Contract Research Organization

Name of company	Business location	Telephone
Atlantic Research Group	2421 Ivy Road, Suite 200, Charlottesville, VA, 22903	434-220-9380

2. BACKGROUND OF CLINICAL STUDY

Neutropenia is a common side effect of cytotoxic chemotherapy used to treat certain diseases such as cancer. Neutropenia may result in suspension and dose reduction of chemotherapy to limit the clinical efficacy of chemotherapy. Furthermore, neutropenia may lead to serious and life-threatening infections, which may prolong the period of hospitalization and require intensive antibiotic therapy.

The primary method currently used to prevent or reduce the severity of chemotherapy-induced neutropenia is to inject bone marrow growth factor such as granulocyte colony stimulating factor (G-CSF; for example, filgrastim, tbo-filgrastim, pegfilgrastim) and granulocyte macrophage colony stimulating factor (GM-CSF, e. g., Sargramostim).

However, up to 30% of patients treated with granulocyte colony stimulating factor have developed various toxic reactions[2] such as skeletal pain, rare allergic reactions, acute respiratory distress syndrome, alveolar hemorrhage, and hemoptysis. Even if granulocyte macrophage colony stimulating factors are administered, it will lead to toxic reactions including muscle pain, facial flushing, low grade fever, headache, skeletal discomfort, nausea, dyspnea, and edema. Although most adverse events related to conventional therapies are mild to moderate and reversible[2,3], it is necessary to develop an adjuvant therapy that can be administered easily without the burden of secondary adverse events to cancer patients who are exposed to various adverse reactions from the administration of cytotoxic chemotherapy alone.

EC-18 (1-palmitoyl-2-linoleoyl-3-acetyl-rac-glyerol [PLAG]) belongs to the chemical family of monoacetyl diacylglycerides (MDAGs) and this substance is discovered in antler, bovine mammary gland, and also in nature, such as sac fungi. EC-18 exists as (R)- or (S)- type asymmetric chiral isomers and the EC-18 agent used in this clinical study is racemate that has the same ratio of isomers of (R) - and (S)[4]
EC-18 was marketed in Korea in 2014 as health functional food product (ROCKPID®). ROCKPID 500 mg, twice-a-day oral use was approved by the Ministry of Food and Drug Safety as a health functional food product for the purpose of improving immune function.

Cytotoxic chemotherapy using anticancer agents generally causes mitochondrial damage and oxidative stress in normal cells and cancer cells. Through this, the signal transducer and activator of transcription 3 (STAT3) is activated and production of chemokine that activates and promotes the extravasation of neutrophils is increased, resulting in clinically problematic chemotherapy-induced neutropenia (CIN). EC-18 effectively reduces the activation of STAT 3 and expression of chemokines such as (C-X-C motif) ligand 2 (CXCL2), CXCL8, etc. that are induced by chemotherapy.[5,6,7] Neutrophils and intercellular adhesion molecules are directly involved in the extravasation of neutrophils. EC-18 also effectively reduces adhesion molecules such as MAC-1, E-selectin, L-selectin, and P-selectin, which are induced by chemotherapy. Therefore, EC-18 is expected to prevent CIN or decrease the degree of CIN during the course of anticancer chemotherapy.

The nonclinical safety test results showed that, EC-18 did not affect the cardiovascular, central nervous system, or respiratory system in animals administered with EC-18 orally up to a maximum dose of 2000 mg/kg. Moreover, in 6-month and 9-month repeated oral dose studies using rats and dogs, the no-observed-adverse-effect-level (NOAEL) was the maximum test dose

of 2000 mg / kg. There were also no significant changes (inhibition or induction) of the cytochrome P450 enzymes by in vivo EC-18 administration, and genotoxicity results confirmed in a series of in vitro and in vivo studies and pre-embryogenesis test in rats and rabbits were also negative. There were also no significant changes (inhibition or induction) of the cytochrome P450 enzyme system by in vivo EC-18 administration, and genotoxicity results confirmed in a series of in vitro and in vivo studies and pre-embryogenesis test in rats and rabbits were also negative.

EC-18 was evaluated in five clinical studies. The first clinical trial (using EC-18 soft gel) was a double-blind, placebo-controlled, randomized trial in healthy volunteers conducted from October 31, 2012 through January 31, 2013 in Korea. Effectiveness on immune function was assessed in healthy subjects by administering EC-18 500 mg soft gel twice daily for 4 weeks. Thirty seven subjects received EC-18 and 38 subjects received placebo. The number of white blood cells (WBCs), immunohistochemical markers, differential cell counts, T-cell subpopulation percentages, immunoglobulin levels, and C3 and C4 levels, cytokines released from cultured monocytes, in vitro lymphocyte function and natural killer cytotoxic activity were verified. Although both EC-18 and placebo groups showed changes in some of the parameters from baseline to week 4, the immunoregulatory indices of the EC-18 treated group showed the tendency to improve the differences between the two treatment groups in a statistically different manner. However, the immunologic improvement confirmed in this study was the assessment result of EC-18's immunological improvement only in vitro with the blood sample.

Based on this, a small-scale, phase 2 preliminary pilot study was conducted in Korean patients with metastatic or locally advanced pancreatic cancer for the assessment of efficacy of EC-18 in preventing severe neutropenia. Sixteen subjects receiving gemcitabine 1000 mg/m^2 and erlotinib 100 mg at Day 1, 8, and 15 of the 4-week cycle were administered with the oral dose of 500 mg EC-18 (ROCKPID formulation) daily for 2 days. Subjects who received EC-18 were compared to 32 subjects in placebo-control group who have been enrolled sequentially by matching age, functional status, comorbidity, disease severity, and type and dose of anticancer drugs. It was confirmed that 10 out of 16 subjects (62.5%) who received EC-18 had Grade 1 neutropenia (Grade 1 absolute neutrophil count [ANC] 1.5 approximately <2.0 x 10^9/L) versus 6 of the 32 subjects (18.8%) in the control group. Three of 16 EC-18 subjects administered EC-18 (18.8%) and 13 of 32 control group subjects (40.6%) had Grade 2 neutropenia (Grade 2 ANC 1.0 to <1.5 x 10^9/ L), and 3 out of 16 subjects administered with EC-18 (18.8%) and 11 out of 32 subjects (34.4%) in the control group had Grade 3 neutropenia (Grade 3 definition: ANC 0.5 approximately < 1.0 x 10^9/L). In the EC-18-administered subjects, Grade 4 neutropenia (definition of grade 4: ANC <0.5 x 10^9 /L) did not occur in the EC-18-administered subject group, and it occurred in 2 subjects (6.3%) in the control group.

Three phase 1 clinical studies completed in healthy male and female volunteers (EC 18-001: SAD, EC-18-101: SAD and MAD, and EC-18-102: Food effect), safety, tolerability, pharmacokinetics and pharmacodynamics of single-dose EC-18 from 500 to 4000 mg were evaluated. There were no significant changes or differences in parameters of pharmacodynamic effects (total leukocyte count, absolute neutrophils, eosinophils, lymphocytes (including CD4 and CD8, monocytes, neutrophils, and red blood cells [RBC]) observed between EC-18 and placebo. Plasma concentration of EC-18 were generally increased for 6 - 12 hours post-dose and rapidly decreased after reaching the maximum concentration. The concentration dropped below

the limit of quantification after 24 hours following administration. The plasma exposure to EC-18 was low and variable, and was not dose-dependent in the studied dose range.
In a food effect study conducted in healthy volunteers, EC-18 was safe and showed superior tolerability with both fasting and high-fat diets up to 2000 mg. All adverse events observed were at the level of mild or moderate, were not dose-dependent, and no serious adverse events were observed. There were no clinically significant changes in lab test values, electrocardiograms, and vital signs, and there was no tendency for differences between fasting and high-fat diet group. EC-18 plasma exposure (C_{max} and AUC) was significantly greater (5 to 15-fold) in the high-fat diet group than that in the fasting group and was observed in increase in a dose-proportional manner.
In all five clinical studies, EC-18 was well tolerated and abnormal observations in clinical laboratory results were minor as well. One subject had hepatitis and completely recovered within a few days.

Based on the outcomes of the EC-18 clinical development program and human safety monitored for 2 years post-marketing surveillance of ROCKPID, this study will be conducted to evaluate the efficacy of EC-18 on severe neutropenia in cancer patients who receive chemotherapy.

3. PURPOSE OF THE CLINICAL STUDY

3.1. Primary Objective:

The primary objective is to demonstrate safety and significant recovery of grade 4 neutropenia when EC-18 is administered to patients with relapsing or metastatic breast cancer whose risk level for febrile neutropenia is low and who are receiving second line or higher chemotherapy (including endocrine therapy) that incorporates doxorubicin/cyclophosphamide. The first 15 days of daily absolute neutrophil count and the period to recover the number of absolute neutrophil to 1.5 x 10^9 / L will be analyzed as primary endpoints.

3.2. Criteria of failure in and discontinuation of the treatment::

Failure in EC-18 treatment is determined and discontinuation of EC-18 treatment is considered by the following methods during the chemotherapy period.

1. List and identify the properties of all significant infectious adverse events requiring systemic antibiotics or inpatient therapy; Subjects who have been identified to have these serious adverse events are considered treatment failures regardless of the treatment group.
2. Febrile episode (oral temperature > 100.6 °F [38 °C]) with neutropenia (all of severity grade); subjects with febrile neutropenia are considered secondary treatment failures. In the event of febrile neutropenia, rapid-acting granulocyte colony-stimulating factor rescue therapy may be performed according to the judgment of the investigator and standard of care. If the subject has received interventional treatment with a rapid-acting granulocyte stimulating factor (as recommended by the 2015 ASCO clinical practice guideline update) based on the investigator's judgment and standard of care, administration of study drug will be discontinued.
3. Clinical symptoms and clinically significant abnormal laboratory results will be evaluated to compare severity, duration, and sequelae of all adverse events associated with EC-18. Subjects who have been withdrawn from the study early due to adverse events will be regarded as treatment failures.

3.3. Secondary Objective

To determine the maximum tolerated dose (MTD) and confirm the safety of EC-18.

3.4. Definition of Dose-Limiting Toxicity (DLT)

The DLT will be evaluated throughout the duration of the study. The level of toxicity will be documented in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) (v4.03) for the National Cancer Institute (NCI) regarding adverse events.

- Febrile neutropenia or neutropenia (≥ Grade 3), neutropenia with infection (≥ Grade 3), or Grade 4 neutropenia persisting for ≥ 4 days; Grade 4 thrombocytopenia (or Grade 3 thrombocytopenia with marked bleeding symptoms);

- If non-hematologic toxicity associated with the treatment of Grade 3 or 4 occurs, nausea, vomiting, diarrhea, and elevation of AST and ALT will be considered dose-limiting toxicity if any of the following applies:
  - Grade 3 or higher nausea, vomiting, or diarrhea for ≥72 hours even after appropriate treatment is provided
  - Grade 3 or higher increase of ALT or bilirubin regardless of duration
  - An ALT elevation of ≥ Grade 2 (≥ 3.0 x ULN) with a grade 2 or higher total bilirubin elevation (> 1.5 X ULN)
- If Grade 3 hypersensitivity lasts for ≥ 24 hours, or if dosing is not possible at the full dose of chemotherapy, or if Grade 4 hypersensitivity reaction occurs regardless of duration
- If there are TEAE or associated significant laboratory findings resulting in delay of administering chemotherapy agent by one week or longer.
- Severe or clinically significant infection of grade 3 or higher

In order to consider adverse events as DLTs, it should be clinically significant and at the same time its relationship with the study drug should be at least "Possibly" or more; therefore, dose-related fever ≥ grade 3 will not be considered as the DLT.

All adverse events assessed as a DLT, regardless of severity, are an adverse event of special interest (AESI) according to the SAE reporting requirements and should be reported within 24 hours from the time when the investigator becomes aware of them.

Administration of EC-18 should be discontinued in all cases of DLT. This includes all of the above and non-hematologic toxicities (≥ Grade 4) for which causes have not been clearly identified, or non-hematologic adverse events above grade 3 that persist or recur after EC-18 discontinuation.

3.5. Definition of Dose Elevation and Maximum Tolerated Dose (MTD)

The purpose of dose escalation is to confirm the safety and toxicity characteristics of EC-18 in a limited number of subjects. By utilizing the standard 3 + 3 design, four dose cohorts (500 mg, 1000 mg, 1500 mg, 2000 mg) of three subjects each may be enrolled.

Following confirmation of safety by 1-week monitoring of a subject in a cohort, the next subject will be enrolled in the cohort. After the third subject has completed the 21-day DLT assessment, a Data and Safety Monitoring Committee (DSMC) meeting will be convened to determine how to proceed to the next dose level after the consent from the investigator, sponsor and medical monitor (see Section 3.5.1).

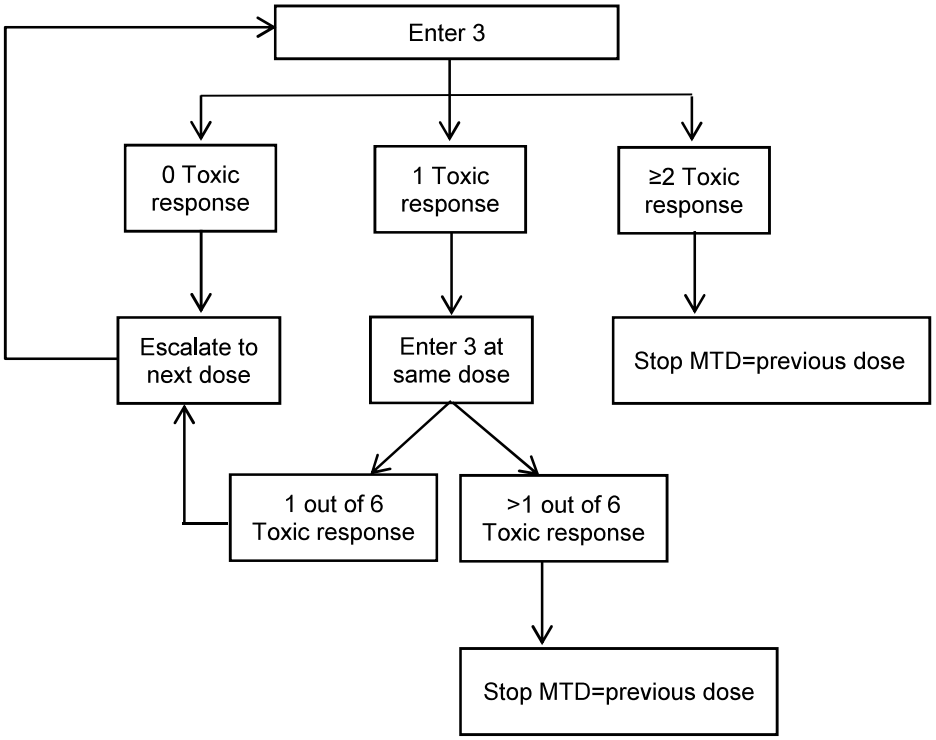
If one of 3 subjects develops a DLT, 3 additional subjects will be recruited and receive the same dose; thus, a total of 6 subjects will be included in a given cohort. If no DLTs are observed, the dose will be escalated to the next dose level. The dose level at which a DLT is observed in more than 2 of 6 subjects will be defined as exceeding MTD, and 3 additional subjects will be administered the previous dose level. The MTD is defined as the highest dose at which no more

than 1 of 6 subjects had a DLT. Subjects with a DLT must be discontinued from the study. The dosing scheme for dose-limiting toxicity management is shown in Table 1 and Figure 1.

Table 1: Dosing Scheme for Management of Dose-limiting Toxicities

Number of subjects developing DLT / Total number of subjects in a cohort	Actions and plan of addition of subjects
0/3	Dose escalation
1/3	Addition of 3 subjects to the current cohort (expansion of the cohort)
≥2/3	Halt of dose escalation
1/6	Dose escalation
≥2/6	Halt of dose escalation

Figure 1: Decision Tree of 3+3 Design, Dose-escalation



If hepatotoxicity is suspected, a liver function test will be performed during the blood chemistry test within 72 hours of discovery to determine the status of recovery from hepatotoxicity. If the ALT elevation is ≥ Grade 2 (≥ 3.0 x ULN) with an elevation in total bilirubin ≥ Grade 2 (> 1.5 X ULN), the subject will be discontinued from treatment and with a liver specialist will be consulted. The final decision on causality and severity pertaining to the study drug will be determined by the DSMC based on comprehensive clinical judgement of the specialist.

Safety data for the purpose of determining dose escalation will include laboratory tests, all adverse events, cardiovascular assessments, and other related data collected. The dose escalation scheme is shown in Table 2.

Table 2. Dose Escalation Scheme

Cohort	EC-18 Dose
1	500 mg
2	1000 mg
3	1500 mg
4	2000 mg

The 21-day administration period was designed to assess the response to toxic and therapeutic effects. EC-18 treatment is administered continuously for 21 days unless the risk of infection (assessed by ANC values) is unacceptable, or disease progression occurs, or other unacceptable adverse events occur. After 21 days of EC-18 treatment, all subjects will be followed for the 4-week safety assessment.

3.5.1. Data Safety Monitoring Committee (DSMC)

The DSMC will consist of at least three medical doctors, all experienced in the conduct of clinical trials in oncology. The sponsor medical monitor and at least one of the investigator participating in the study will make a recommendation for dose escalation based on their review of safety data for the preceding cohort and following the guideline established in this protocol related to DLT. Details on the safety assessments, frequency of review, meeting schedules will be documented in the Medical Monitoring Plan.

4. CLINICAL STUDY DRUG

4.1. Study Drug

- Product name: EC-18 Softgel Capsules
- Manufacturer: Enzychem Lifesciences Corporation
- Dosage Form and Appearance: Chocolate-colored soft capsules containing clear or light yellow transparent liquid
- Pharmaceutical Ingredients and quantity: 1-palmitoyl-2-linoleoyl-3-acetyl-rac-glyerol (PLAG) 500mg and α-tocopherol 1mg
- Storage method: Store at room temperature (15 to 30 °C)

4.2. Control Drug

Not applicable.

4.3. Chemotherapeutic agents

Doxorubicin and cyclophosphamide are stored under the given storage conditions.

4.4. Usage and Dose of Study Drugs

Following a 4- week screening period, a 3-week dosing period will commence followed by a 4-week safety follow-up period. In this study, combination therapy consisting of one cycle of doxorubicin and cyclophosphamide (AC) should be administered on Day 1. The pharmacological/hematological efficacy of EC-18 will be evaluated in subjects who have received one standard AC combination therapy.

Three patients in each group will be administered one of four doses of EC-18 based on the cohort to which they are assigned (500, 1000, 1500, or 2000 mg) from Day 1, the first day of dosing. Doses will be administered with breakfast.

EC-18 administration will be discontinued upon completion of the 3-week treatment. Except for Days 3 and 4, a daily check on CBC and differentiated blood cell count will be done for 15 days during the first cycle of chemotherapy or until the ANC is restored to $\geq 1.5 \times 10^9$/L. Safety evaluation and monitoring of adverse events and concomitant medication will be conducted throughout the clinical study.

4.5. Basis for Clinical Study Drug Dosage

The validity of the planned initial drug dose in this study was established from the following results: (1) Stability profile in non-clinical safety studies with no or minimal change in adverse events or lab test readings; (2) relative exposure amount obtained by comparing the plasma concentration data obtained in the Phase I study in human subjects; (3) exposure information in clinical studies on single and multiple doses up to the dose of 4000 mg daily and in clinical studies in which it was administered with meals; (4) evaluation of available pharmacokinetic data; (5) clinical safety data showing no significant clinical ADR at all dose levels; and (6) pseudomonas aeruginosa infected mouse model showed a better survival rate in the EC-18 group compared with the control group.

- Safety profile in non-clinical study: No toxicity was observed in the 6-month / 9-month repeated dose toxicity study in rats and dogs, and no harmful effects on fertility / reproductive organs were observed in any of the toxicity tests. NOAEL from the 6-month/9-month repeated dose toxicity study in rats and dogs was 2000 mg/kg /day.
- Exposure and dose equivalence in nonclinical studies: The maximum plasma concentration (C_{max}) and exposure level (plasma concentration versus time curve area, AUC) measured on Day 91 in the 13 week repeated dose toxicity study for dogs were 1225 ng/mL and 10838 ng *h/mL. In the 6-month and 9-month repeated dose toxicity studies in rats and dogs (Study No. B13945 and B13946), the dose of 2000 mg/kg/day which is the limiting dose recommended by International Conference on Harmonization of Medicines (ICH) M3 (R2) was administered to animals. This resulted in up to 6-12 times greater than the corresponding maximum C_{max} (= 263 ng /mL) and exposure level (= 561 ng*h/mL) measured in human pharmacokinetic / food

impact studies (study EC-18-102) serum / plasma C_{max} (50 ng / mL in rats; 1520 ng / mL in rats) was induced, as well as exposure levels (199 ng * h / mL in rats; 6947 ng*h/mL in dogs). In this study, EC-18 as a single oral dose of 2000 mg was administered in the fasting condition and reached the highest EC-18 exposure level determined in all clinical studies on EC-18 to date.

- Exposure in previous clinical studies: EC-18 was administered at the single, maximum dose of 4000 mg in two single-dose escalation studies conducted in United States and Korea and at multiple doses for up to 14 days in a multi-dose escalation study in Korea. A significant increase in plasma exposure (C_{max} and AUC) was observed in the postprandial condition compared with the fasting condition in the pharmacokinetic/food effect study (Study EC-18-102) in which a single dose of EC-18 was administered up to 2000 mg. Therefore, the sponsor proposes the dose of EC-18 2000 mg once daily for this phase 2 study. At this dose, the plasma concentration at this dose is expected to exceed the exposure to humans that was determined in the previous studies and to maintain the safety factors for plasma exposure determined in non-clinical studies.
- Evaluation of available pharmacokinetic data: Evaluation of available PK data: In the single ascending dose studies (EC-18-001, EC-18-101, Part 1), the observed plasma concentration of EC-18 was low and highly variable; therefore, assessment of the final plasma half-life was not possible in most subjects. However, the plasma concentration of EC-18 fell below the limit of quantitation until 24 hours after administration. In the multiple ascending dose study (EC-18-101, Part 2), the EC-18 plasma concentrations (C_{max} and AUC) were dose dependent (but not linear) in the dose range assessed in this study. For all the doses studied, accumulation did not occur at steady state after multiple administrations. Although the plasma half-life of EC-18 could not be accurately estimated for most subjects in the single-dose escalation study, the plasma concentration of EC-18 was reduced below the limit of quantitation until 24 hours after administration (Day 1) in all subjects in all dose groups. No evidence of accumulation was observed in the non-clinical and repeated treatment toxicity tests where exposure and plasma concentration were significantly higher.
- Clinical safety profile: In general, tolerability of EC-18 was very good and the treatment-emergent adverse events (TEAEs) observed in each of the three tests were mild to moderate. It was demonstrated that the observed TEAE was not related to the dose and serious adverse events (SAEs) were not observed in any of the tests. In single-dose studies, transaminase agent and bilirubin were elevated for 6 days in one subject, but there was no evidence of hepatic ultrasonography in the follow-up tests. All abnormal laboratory findings were normalized over several weeks.
- Pseudomonas aeruginosa-infected mouse model: An in vivo mouse model of infection with Pseudomonas *aeruginosa* K demonstrated that administration of EC-18 did not increase the severity of infection. In fact, the bacteria clearance was significantly faster when dosed with EC-18 compared to the control, suggesting that

EC-18 did not compromise the innate immune response necessary to fight off infection.

4.6. Packaging and Labeling of Investigational Products

All study drugs used in this study are prepared, packaged, and labeled in accordance with the packaging company's standard operating procedure guidelines, the Pharmaceutical Manufacturing and Administration (GMP) Guidelines, and the ICH Guidelines for Clinical Trial Management (GCP).

The complete formulation of EC-18 is described in the EC-18 Investigator Brochure.

EC-18 is supplied as a 500 mg soft capsule for oral administration.

Study drugs are packaged and sent to the pharmacy of each study center. The outer packaging is labeled with at least the following information:

Containers or labels on medicines used in the clinical study include the following information in accordance with the relevant laws and regulations for pharmaceuticals for clinical studies.

- A statement indicating that study medication is intended for clinical trial purposes only (e.g., “For clinical study”)
- Name or identification labeling of the study drug
- Batch number or code number to identify the contents and packaging operations
- Name, address and telephone number of the sponsor
- Use-by (expiration) date or re-testing date
- Storage conditions
- "Keep out of reach of children.”
- Subject identification number, study drug number, and visit number
- A reference code that identifies the clinical study

4.7. Storage of Investigational Products

All study drugs should be stored safely by the pharmacist/designated dispenser at the study center in a secure area with a lock and restricted access that is allowed to the study team only in accordance with the ICH, GCP, and US Food and Drug Administration cGMP guidelines. EC-18 capsules should be stored in containers provided at -20-25 °C (store at USP controlled room temperature, excursions between 15-30 °C allowed) and protected against extreme conditions of temperature, light, and humidity. These storage conditions differ from those listed in the current Investigator’s Brochure (IB), but will be revised to those shown here with the next IB update.

The investigator or designated person must maintain accurate records of receipt of the study drugs including the date of receipt of the study drug, lot number, expiration date, amount received, packaging status, and placement of all study drugs.

4.8. Dispensing of Investigational Products

Pharmacists/designated dispensers at the study site are responsible for issuing the study drugs. The investigator is responsible for ensuring that the study drug is issued only as specified in the protocol. The EC-18 study drug should be given orally in the morning with food.

4.9. Accountability of Investigational Products

The study site should ensure that study drugs are not supplied to persons other than the subject under the conditions specified in the protocol (i.e., delivery to the study center, the study center's inventory list, use for subjects, disposal, etc.) by maintaining accurate management of receipts and disbursements records to ensure that they are issued in accordance with ICH, GCP and GMP guidelines. The investigator/designated person must immediately notify the sponsor of any quality issues raised in relation to the study drug. If such a situation occurs, the investigator (with the sponsor) will investigate, perform, and document all necessary corrective actions required.

4.10. Handling and Disposal of Investigational Products

Study drug is recorded in the drug inventory record (including the record of the study drugs sent to an investigator and the records generated by the study center). The monitor reviews the stock form during the study period and at the end of the study. The investigator or authorized person will resolve all questions raised by the review of the study monitor and sign the drug inventory record. The investigator must maintain a copy of all drug inventory records.

All remaining used/unused study drugs should be maintained until the final guideline of the study monitor personnel is provided.

Enzychem Lifesciences Corporation will provide the study center with detailed instructions on how to return the study drugs. Handling and disposal of study drugs after all treatments will be done in accordance with ICH, GCP and GMP guidelines.

5. TARGET DISEASE

Subjects with advanced breast cancer receiving chemotherapy with a low risk level of febrile neutropenia will be enrolled in the study.

6. INCLUSION AND EXCLUSION CRITERIA

6.1. Inclusion Criteria

Subjects will be enrolled in the study if they meet all of the following criteria:

1. Women ≥19 years of age
2. Subjects who have voluntarily signed the informed consent prior to the screening tests to participate in the study
3. Subjects who have been diagnosed as adenocarcinoma of the breast and relapsed after adjuvant or primary (neoadjuvant) chemotherapy, and thus through history have been confirmed to be candidates for chemotherapy of second line or higher (including hormonal therapy) combined with doxorubicin and cyclophosphamide to treat relapsed or metastatic disease.
4. Subjects with adequate organ function based on the following clinical laboratory values in the final examination performed within 14 days prior to dosing:
   - Neutrophil count (ANC): ≥1,500/mm^3
   - Platelet count: ≥10.0×10^4/mm^3
   - Hemoglobin: ≥9.0 g/dL
   - AST, ALT: ≤3.0 x ULN
   - Serum total bilirubin: ≤1.5 mg/dL
   - Serum creatinine: ≤1.5 mg/dL
5. Subjects whose Eastern Cooperative Oncology Group (ECOG) performance score is 0-1.
6. For women of child bearing potential, subjects should have willingness to use acceptable contraceptive methods during the entire clinical study period.
7. Subjects who are capable of understanding the overall procedure of the clinical trial and are willing to participate in compliance with all test procedures.

6.2. Exclusion criteria

Subjects who do not meet all of the following criteria will be excluded from participation in the study.

1. Subjects with active and inactive hepatitis, patients with HIV, or other uncontrolled infectious disease.
2. Subjects who received radiation therapy within 4 weeks of dosing.

3. Subjects who have been diagnosed within 5 years with other types of cancer except for those who have been appropriately treated for superficial non-melanoma skin cancer or cervical intraepithelial neoplasia.
4. Subjects with a history of intolerance for granulocyte colony stimulating factor treatment
5. Subjects who are expected to show hypersensitivity to the study drug or its ingredients
6. Subjects with a positive urine pregnancy test result prior to the screening visit or the first administration of the study drug
7. Subjects who took any other study drug used in a clinical trial within 30 days prior to the screening visit.
8. Clinically significant unstable medical abnormality; psychiatric disorder, chronic disease, alcohol or drug use disorder, or other significant biological, psychological, or social factor, which in the investigator's opinion, unfavorably affects the risk-benefit ratio of study participation is likely to interfere with satisfactory study completion or confound its outcome.
9. Subjects with unstable heart disease (Example: Congestive heart failure, arrhythmia, symptomatic coronary artery disease); Myocardial infarction within 6 months before initiation of the study.
10. Subjects with left ventricular ejection fraction (LVEF) < 50% at screening.
11. Significant neurological or psychiatric disorders including dementia or seizures.
12. Subjects with poorly controlled hypertriglyceridemia (>500mg/dL) with use of hypolipidemic agents.
13. Subjects with poorly controlled diabetes (fasting glucose> 150 mg / dL or HbA1c ≥ 8%).
14. Subjects who have received systemic chemotherapy with doxorubicin anticancer agent to treat metastatic or recurrent breast cancer
15. Subjects with Grade 2 or higher peripheral sensory neuropathy prior to the screening visit or first dosing of the study drug
16. Subjects who have undergone significant gastrectomy with intractable nausea and vomiting, chronic gastrointestinal disease, or clinically significant sequelae, which would interfere with proper absorption of the study drug
17. Subjects who were administered with systemic antibiotics within 14 days prior to administration of the study drug
18. Subjects who are currently receiving trastuzumab

7. CLINCAL STUDY PERIOD

The study is expected to be approximately 24-months in duration.

8. DESIGN AND METHOD OF THE CLINICAL STUDY

8.1. Study Design Overview

This study will utilize a non-randomized, open-label 3 + 3 dose escalation design. Three subjects in each group will be administered study medication 30 minutes after a regular breakfast.

Since oral administration of EC-18 has been shown to maintain high systemic exposure and low variability when administered orally with meals, all subjects are instructed to take EC-18 after meals. The initial dose of this study was carefully reviewed by the sponsor, external experts, as well as by FDA's Division of Hematology Products. The rationale for the initial dose is described in Section 4.5 above. The four doses planned are 500 mg, 1000 mg, 1500 mg and 2000 mg. In the event of occurrence of a DLT, three subjects will be added to the corresponding dose group. The DSMC will review the safety and pharmacodynamic activity of each dose group to determine if it can be increased.

Safety and drug tolerability during the entire course of the study will be monitored through physical examination, 12-lead electrocardiogram (ECG), vital signs, TEAEs, and clinical laboratory test results.

8.2. Subjects' participation period

- 7 weeks (3 weeks of administration period and 4 weeks of safety follow-up investigation);
- Effectiveness of EC-18 is monitored for 3 weeks (1st cycle) and safety is monitored for 7 weeks by adding 4 weeks of follow-up observation period to the 1st cycle.

8.3. Number of subjects

A total of 12 subjects are planned initially for enrollment: 4 dosing cohorts (500 mg, 1000 mg, 1500 mg, and 2000 mg), each enrolling 3 subjects initially. If a DLT occurs in any cohort, an additional 3 subjects will be enrolled and administered the same dose, which would increase the number of subjects in a given cohort to 6. If the second DLT occurs in the expanded cohort, no more subjects will be added and dose escalation will be stopped.

8.4. Method of the Clinical Study

Part 1 of this study consists of a screening period (up to 28 days); three weeks of dosing (Day 1 to Day 21) with starting administration of doxorubicin 60 mg /m^2 (Day 1) and cyclophosphamide 600 mg/m^2; and four weeks for safety follow-up observation (Day 22-50) (Table 3). Investigators will administer doxorubicin and cyclophosphamide in accordance with the drug information sheet or the standard procedures of the study center. During chemotherapy treatment period, subjects will receive oral administration of EC-18 once daily after breakfast on Days 1-21.

After the 3-week treatment period, EC-18 administration is stopped and follow-up observation for safety evaluation is performed for an additional 4 weeks (up to 7 weeks after initiation of dosing). It is not necessary to change general subject management or any other additional treatment. Depending on the judgment of the investigator and the standard of care, rapid-acting

G-CSF therapy may be provided for newly developed febrile neutropenia. However, G-CSF is not given prophylactically to the subject during the treatment cycle and safety follow-up period.

The efficacy assessment includes ANC (mean and minimum values), the incidence of neutropenic grade 3-4 (according to NCI CTCAE 4.03 version), the incidence rate of Grade 3 or 4 febrile neutropenia (NCI CTCAE), neutropenia recovery time back to Grade 2 or lower, IV antibiotic administration and the number of hospital admissions, and cases that require interventional treatment using rapid-acting granulocyte colony stimulating factor for those at high risk for side effects of infection or with malignant clinical outcome prediction (according to the recommendations by ASCO clinical practice guideline update 2015) .

For 15 days after starting chemotherapy, the CBC is performed and the ANC is assessed daily or more frequently if it is determined to be clinically necessary for the safety of the subject. Subjects who develop Grade 3 or higher infection should stop taking the drug regardless of their neutropenia status.

During the entire study period, the total volume of blood collected is around 70 mL that includes CBC 13 times or more, serum chemistry, blood coagulation 4 to 5 times, and 1 time of infection evaluation.

Safety and tolerability throughout the study period will be monitored through physical exams including vital signs, adverse events, electrocardiograms (12-lead ECG), and clinical laboratory tests. The 12-lead ECG is recorded on Day 1 and measured again on Day 22, and Day 50 to evaluate electrocardiographic parameters, including PR and QTc. The evaluation schedule of this study is shown in Table 3.

8.5. Methods of Treatment Group Assignment and Dosing

All subjects in this study begin their standard therapy with doxorubicin and cyclophosphamide on Day 1. Biphasic therapy for breast cancer is given for one cycle for subjects with relapsed or recurred breast cancer. All subjects receive EC-18 every morning. The dose level is sequentially set for every three subjects. To assess the efficacy for ANC recovery and its safety at each dose level, EC-18 is continuously administered during the treatment cycle.

8.6. Rules for Discontinuation of Study Medication Administration

Subjects who participate in the study may stop their study participation due to adverse events, lack of effects or for any other personal reasons. Data and Safety Monitoring Committee, Institutional Review Board or regulatory authorities may recommend that the sponsor discontinue the study at any time regardless of reasons. Other discontinuation rules on stopping drug administration include frequent fatal or life-threatening infections in the treatment group, drug-induced hepatotoxicity, or other unanticipated serious adverse events.

8.7. Concomitant Contraindications and Treatment

EC-18 is not metabolized by liver microsomes and cytochrome P450 (microsomal/CYP450) drug metabolizing enzymes. In addition, EC-18 does not inhibit the major CYP450 drug metabolizing effects. The dose and/or safety assessment of treatments requiring administration to the subject will not be affected. However, since the following drugs and treatments cannot rule

out the possibility of affecting the safety or efficacy of the study drug, they are prohibited to be used during the study period and during the additional period in which combination therapy is prohibited.

1. Radiation therapy that may affect bone marrow function.
2. Clinical study drugs other than chemotherapy agents specified in this protocol.
3. Systemic prophylactic antibiotics within 14 days prior to administration of the study drug
4. Combination therapy with biologic agents such as Trastuzumab (Herceptin®) etc. to treat the target disease
5. Prophylactic G-CSF

Information on the contraindication of concomitant use of doxorubicin and cyclophosphamide, which are anticancer chemotherapy agents, is described based on approved drug information. Please refer to Appendix 1 and Appendix 2 for each product.

8.8. Randomization and Blinding Procedures

Subjects will be assigned to treatment sequentially. This study is open-label.

8.9. Drug Compliance

If it is discovered on the scheduled date of visit that the subject is taking the medication outside of the accepted medication compliance of the prescribed medication, the investigator should explain the subject on the importance of drug compliance and instruct subjects to take the study drug properly.

Study drugs should be dispensed under the supervision of the investigator/pharmacist as specified in the protocol.

Sufficient quantities of study drug will be provided for the study and the subject will be trained to return the remaining drugs and packages at the next visit. The subjects will be issued with a subject diary and provided an explanation on how to complete the diary so that they can record their drug intake status daily along with any side effects of nausea and vomiting.

In order to confirm compliance with taking the study drug, the investigator checks the number of drugs prescribed and the number of drugs actually taken along with the dosing diary.

The likelihood of the anticancer chemotherapy regimens given to the subjects in this study to induce vomiting is moderate. In addition, since this study is planned to administer the study drug with meals after Day 1 in which doxorubicin and cyclophosphamide are administered, in order to improve the patient's compliance with the drug, minimize the inconvenience, and more accurately evaluate the safety and efficacy of the drug for evaluation on all subjects. In accordance with the criteria set forth in the Management Standards for Nausea and Vomiting, the prophylactic antiemetic drugs are administered for 3 days, and during the following period, the nausea and vomiting are managed according to the recommendations by the Subcommittee on

Antiemetic Substances of the International Tumor Support Therapy Association (Appendix 3). Subjects who have had episodes of vomiting will not be administered study drug.

8.10. Study Discontinuation Criteria

Subjects who participate in the study may withdraw from study participation at any time due to adverse events, lack of effects or for any other personal reasons. Each of the study centers assists in ensuring treatment, which is the primary concern of subjects with advanced breast cancer. This study will determine MTD; however, subjects will be monitored closely for safety during the treatment period to minimize risk. Subjects are informed about acceptable neutropenic risks. If the subject has received interventional treatment with a short-acting granulocyte stimulating factor (as recommended by the 2015 ASCO clinical practice guideline update) based on the investigator's judgment and standard of care, discontinue administration of the study drug.

9. OBSERVATION ITEMS, CLINICAL TEST ITEMS, AND EVALUATION SCHEDULE

9.1. Overall Schedule of the Clinical Study

Detailed schedule and evaluation items from Day 1 to Day 22 of the chemotherapy cycle and the evaluation items and daily evaluation of ANC, the primary laboratory endpoints, are described in Table 3. The laboratory test results on safety are reported to DSMC at the end of the EC-18 administration cycle for 3 or 6 subjects per group.

9.2. Visit Schedule

9.2.1. Screening Visit (Days -28 to -1)

After completing the written informed consent, subjects who meet the selection/exclusion criteria are recruited through taking of medical history, physical examinations, and laboratory tests. The following table describes the recommended timing for each laboratory test measurements to be taken.

9.2.2. Day 1 Visit, First Treatment Visit

Subjects will visit the clinic while fasting, receive physical examinations and laboratory test items and then the applicants who are eligible according to the selection/exclusion criteria will be enrolled in their respective dosing cohort. EC-18 will be administered 30 minutes following breakfast.

The chemotherapy agents taken by the subjects in this study have a moderate risk of inducing chemotherapy related nausea and vomiting and if the subjects do not use antiemetic agents, they may have nausea and vomiting symptoms. Since this study was designed to take the study drugs after meals, appropriate anti-antiemetic agents (see Appendix 3) should be administered prophylactically to all subjects in accordance with the 2016 National Comprehensive Cancer Network guidelines. In the rare case, where a subject's dietary intake is limited, 1 bottle of Slim Fast (a commercial creamy milk chocolate drink with a calorie content of 220 cal, fat / cholesterol / carbohydrate / protein supplemented with vitamins) or an equivalent product) can be substituted for the meal. Issue a subject diary to each subject and explain the method for completing it.

After that, administer doxorubicin and cyclophosphamide in accordance with both the general standard procedures and the Drug Information Sheet (See Appendix 1 and Appendix 2).

9.2.3. Day 8

Study medication will be administered after breakfast every day. During the outpatient visit, vital signs, combined medication surveillance, body weight measurement, physical examination, laboratory tests, and evaluation of TEAEs are performed.

9.2.4. Day 15 Visit

Study medication will be administered after breakfast every day. At the time of outpatient visit, vital signs, body weight measurement, physical examination, laboratory tests and investigation of combined medications are carried out.

9.2.5. Day 22 and Day 50 Visits

On Day 22 and Day 50, outpatient visits are made and vital signs, weight measurement, physical examination and laboratory test, electrocardiogram, chest X-ray test are performed.

9.2.6. Evaluation Schedule

A schedule of assessments in provided in Table 3.

Table 3: Study Flow Chart

Assessment	Screening	Treatment Phase				
	Week -4 to -1	Week 1	Week 2	Week 3	Week 4	Week 8[k]
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 50
	Visit 1	Visit 2	Visit 3 (±2 days)	Visit 4 (±2 days)	Visit 5 (±2 days)	Visit 6 (±2 days)
Informed consent	X					
Randomization		X				
Inclusion/exclusion criteria	X	X				
Medical history	X					
ECG [a]	X	X[b]			X	X
LVEF	X					
Chest X-ray	X				(X)	X
Concomitant medications	X	X	X	X	X	X
Weight and height [c]	X	X[c]	X[c]	X[c]	X[c]	X[c]
Vital signs	X	X	X	X	X	X
Physical examination	X[d]	X[e]	X[e]	X[e]	X[e]	X[e]
ECOG performance status	X	X			X	X
CBC with differential [f]	X	daily			X	X
Serum chemistry	X	X[b]	X	X	X	X
Coagulation tests	X	X[b]	X	X	X	X
Urinalysis	X					X

Footnotes appear on the last page of this table.

Table 3: Study Flow Chart

Assessment	Screening	Treatment Phase				
	Week -4 to -1	Week 1	Week 2	Week 3	Week 4	Week 8[k]
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 50
	Visit 1	Visit 2	Visit 3 (±2 days)	Visit 4 (±2 days)	Visit 5 (±2 days)	Visit 6 (±2 days)
Urine pregnancy test	X	X[b]			X	X
Virus serology	X					
Reticulocyte count		X	X		X	X
EC-18[g]		Given orally once daily for the first 21 days				
Chemotherapy h		X[i]				
Adverse events	X	X	X	X	X	X
Admission		X[k]		X[k]		

CBC = whole blood count and differential blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group

a. Electrocardiogram (ECG) must be measured prior to drawing blood.
b. As for CBC, serum chemistry, coagulation test, urine pregnancy test, and ECG, if the test was performed within 1 week of randomization (Day 1 visit), it is not necessary to repeat the tests at Day 1 visit.
c. Height is measured only at screening visit.
d. A full physical examination involving the following body parts and systems: Overall appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, chest, lymph node, limb, nerve, skin, and musculoskeletal system.
e. Restricted/focused physical examination including the following parts of the body and systems: Overall appearance, cardiovascular, lungs, abdominal area, chest, lymph node, and areas / systems needed for AE evaluation.
f. CBC includes red blood cell count, hemoglobin, hematocrit, red blood cell count, white blood cell count, differential blood count (absolute and percentage) and platelet count. The CBC and differential blood counts are checked daily until Day 15 or until ANC ≥ 1.5 x 109 / L is restored during the first chemotherapy cycle.
g. The first dose (Day 1) is administered after the assessment at Day 1 visit in hospitals and randomization. All subsequent study drug administration is self-administered at home by the subjects themselves. The subjects should record the date and time of dosing, the status and time of vomiting, and the reasons for missed dose if applicable.

h. Doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2. Prior to the administration of chemotherapy agent, the cumulative dose of anthracycline and LVEF are checked to assess the risk of heart failure. Administration of chemotherapy agents may be postponed until the laboratory test values are restored, but the delay should not exceed a maximum of 3 weeks (21 days).
i. The first cycle (Day 1) of chemotherapy is administered after the assessment at Day 1 visit and randomization. At Day 1, adverse events should be evaluated during and after chemotherapy.
j. Final follow-up is performed at Day 50.
k. Procedures scheduled at Day 1-2 and Day 15-16 are carried out during hospitalization.

9.3. Subject Withdrawal

Subjects who have been withdrawn during the study are required to complete the end of study assessments.

9.4. Unscheduled Visits

During the course of the clinical study, if required, the subject may make additional visits aside from the visits planned in the protocol. For example, if it is suspected that an adverse event has occurred or after an adverse event has occurred, a visit may be made to the study center for follow-up investigations. Visits related to this should be recorded in both the case record form and supporting documentation. In unscheduled visits, physical examinations, vital signs, combined drug surveillance and TEAE evaluations are carried out and other necessary tests can be performed at the discretion of the investigator.

10. ANTICIPATED ADVERSE EVENTS AND USAGE PRECAUTIONS

The adverse events identified in past clinical use experience of EC-18 to date are as follows:

- Diarrhea, abdominal bloating, vomiting, nausea
- Acne, rash, atopic dermatitis, mouth ulcers
- Acute hepatitis, Elevation of liver enzyme level
- Acute tonsillitis, allergic rhinitis, sore throat, cough, runny nose
- Headache, back pain, chest pain, muscle pain, myofascial pain syndrome
- Diabetes, elevated blood sugar, elevated blood triglyceride
- Blood creatinine phosphorylase activity elevation, hematuria
- Leukocytopenia, thrombocytopenia, anemia
- Hypernatremia
- Elevated blood pressure, fever
- Urinary tract infection

The patterns of adverse events identified in each study are summarized in the following sections.

10.1. Study Title: A Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Escalation, Phase I Clinical Trial to Evaluate the Safety, Tolerability and Pharmacokinetic characteristics of EC-18 After Oral Administration in Healthy Male Volunteers

A summary of adverse events from this study is provided in Table 4.

Table 4: Summary of Adverse Events in Study EC18-001

	System Organ Class[a] Preferred Term[a]	Number of Subjects (Percentage of subjects with adverse events)					
		500 mg (N=6)	1000 mg (N=6)	2000 mg (N=6)	4000 mg (N=6)	Placebo (N=8)	Total (N=32)
SAD	**Subject with any adverse event**	**1 (16.7)**	**1 (16.7)**	**2 (33.3)**	**0 (0.0)**	**0 (0.0)**	**4 (12.5)**
	Investigations	**1 (16.7)**	**-**	**1 (16.7)**	**-**	**-**	**2 (6.3)**
	Alanine aminotransferase increased	1 (16.7)	-	-	-	-	1 (3.1)
	Aspartate aminotransferase increased	1 (16.7)	-	-	-	-	1 (3.1)
	Blood glucose increased	-	-	1 (16.7)	-	-	1 (3.1)
	Blood triglycerides increased	1 (16.7)	-	-	-	-	1 (3.1)
	Hepatobiliary disorders	**-**	**-**	**1 (16.7)**	**-**	**-**	**1 (3.1)**
	Hepatitis acute	-	-	1 (16.7)	-	-	1 (3.1)
	Skin and subcutaneous tissue disorders	**-**	**1 (16.7)**	**-**	**-**	**-**	**1 (3.1)**
	Urticaria	-	1 (16.7)	-	-	-	1 (3.1)
MAD	**Subject with any adverse event**	**4 (66.7)**	**5 (83.3)**	**4 (66.7)**	**3 (50.0)**	**4 (50.0)**	**20 (62.5)**
	Gastrointestinal disorders	**1 (16.7)**	**2 (33.3)**	**1 (16.7)**	**-**	**1 (12.5)**	**5 (15.6)**
	Diarrhoea	-	2 (33.3)	-	-	-	2 (6.3)
	Nausea	-	1 (16.7)	1 (16.7)	-	-	2 (6.3)
	Abdominal distension	-	-	1 (16.7)	-	-	1 (3.1)
	Constipation	-	-	-	-	1 (12.5)	1 (3.1)
	Mouth ulceration	1 (16.7)	-	-	-	-	1 (3.1)
	Infections and infestations	**-**	**1 (16.7)**	**1 (16.7)**	**1 (16.7)**	**1 (12.5)**	**4 (12.5)**
	Acute tonsillitis	-	1 (16.7)	1 (16.7)	-	-	2 (6.3)
	Pharyngitis	-	-	-	1 (16.7)	1 (12.5)	2 (6.3)
	Investigations	**1 (16.7)**	**1 (16.7)**	**1 (16.7)**	**1 (16.7)**	**-**	**4 (12.5)**
	White blood cell count decreased	1 (16.7)	-	1 (16.7)	1 (16.7)	-	3 (9.4)
	Blood triglycerides increased	-	1 (16.7)	-	-	-	1 (3.1)
	Respiratory, thoracic and mediastinal disorders	**-**	**2 (33.3)**	**-**	**-**	**2 (25.0)**	**4 (12.5)**
	Oropharyngeal pain	-	-	-	-	2 (25.0)	2 (6.3)
	Cough	-	1 (16.7)	-	-	-	1 (3.1)
	Rhinorrhoea	-	1 (16.7)	-	-	-	1 (3.1)
	Skin and subcutaneous tissue disorders	**2 (33.3)**	**-**	**1 (16.7)**	**-**	**-**	**3 (9.4)**
	Acne	-	-	1 (16.7)	-	-	1 (3.1)
	Dermatitis atopic	1 (16.7)	-	-	-	-	1 (3.1)
	Urticaria	1 (16.7)	-	-	-	-	1 (3.1)
	Blood and lymphatic system disorders	**-**	**1 (16.7)**	**-**	**1 (16.7)**	**-**	**2 (6.3)**
	Anaemia	-	1 (16.7)	-	-	-	1 (3.1)
	Thrombocytopenia	-	-	-	1 (16.7)	-	1 (3.1)
	Musculoskeletal and connective tissue disorders	**1 (16.7)**	**-**	**1 (16.7)**	**-**	**-**	**2 (6.3)**
	Musculoskeletal chest pain	1 (16.7)	-	-	-	-	1 (3.1)
	Myofascial pain syndrome	-	-	1 (16.7)	-	-	1 (3.1)
	Renal and urinary disorders	**-**	**-**	**-**	**1 (16.7)**	**1 (12.5)**	**2 (6.3)**
	Glycosuria	-	-	-	1 (16.7)	-	1 (3.1)
	Haematuria	-	-	-	-	1 (12.5)	1 (3.1)
	General disorders and administration site conditions	**-**	**1 (16.7)**	**-**	**-**	**-**	**1 (3.1)**
	Chest pain	-	1 (16.7)	-	-	-	1 (3.1)
	Nervous system disorders	**1 (16.7)**	**-**	**-**	**-**	**-**	**1 (3.1)**
	Headache	1 (16.7)	-	-	-	-	1 (3.1)

a. System organ class and preferred term: MedDRA (Ver. 18.0)
SAD: single ascending dose, single administration, MAD: multiple ascending dose, once per day for 14 days; 500 mg: single administration of EC-18 500 mg 1 capsule, 1000 mg: single administration of EC-18 500 mg 2 capsules, 2000 mg: single administration of EC-18 500 mg 4 capsules, 4000 mg: EC-18 500 mg 8 capsules

- **Part 1 (single dose group)**
    - Six cases of adverse events occurred in 4 out of 32 subjects (12.5%) who received at least one study drug, and all of the adverse events were not serious.
    - Treatment groups were (1 subject, 16.7%), 1000 mg (1 subject, 16.7%), 2000 mg (2 subjects, 33.3%), 4000 mg (0 subjects, 0.0%), and Placebo Respectively. Among them, the severity of acute hepatitis in subject A3006 subject who belonged to the 2000 mg group was judged to be 'severe'. Other five cases were judged to have “mild” severity and irrelevant to EC-18 and were recovered or resolved without taking any special measures.
    - Subject A3006 was found to have abnormal liver function test results at a follow-up visit, but there were neither subjective/objective symptoms nor any specific findings in gastroenterologic examination, and the subject recovered normally without sequelae and complications. Since subject the drug concentration in A3306 was too low to consider the in vivo exposure to be toxic, it was difficult to see it as an adverse event related to drug exposure caused by dose elevation. Therefore, the investigator and the sponsor decided to continue the clinical study.
    - In addition, there were no clinically significant results in the vital sign, physical examination, and electrocardiogram evaluation of all subjects who participated in the EC-18 single-dose group.
- **Part 2 (repeated dose group)**
    - 30 cases of adverse events occurred in 20 out of 32 subjects (62.5%) who received at least one study drug, and all of the adverse events were not serious. Among them, four cases (12.5%, four cases) were found to be related to EC-18.
    - All of the adverse events were classified as “mild” and most of them were resolved or recovered without taking any special measures.
    - In addition, there were no clinically significant results in the vital sign, physical examination, and electrocardiogram evaluation of all subjects who participated in the EC-18 repeated-dose group.

10.2. Study Title: A Randomized, Open-Label, Single-Dose, Crossover, Phase I Clinical Trial to Evaluate the Effect of Food on the Safety, Tolerability, and Pharmacokinetics of EC-18 after Oral Administration in Healthy Volunteers

A summary of adverse events from this study is provided in Table 5.

Table 5: Summary of Adverse Events

System Organ Class[a] Preferred Term[a]	Number of Subjects (Percentage of subjects with adverse events)									Total (N=36)
	500 mg			1000 mg			2000 mg			
	R05 (N=12)	T05 (N=12)	Total (N=12)	R10 (N=12)	T10 (N=11)	Total (N=12)	R20 (N=12)	T20 (N=12)	Total[b] (N=12)	
Subjects with any adverse event	**1 (16.7)**	**3 (25.0)**	**4 (33.3)**	**1 (8.3)**	**0 (0.0)**	**1 (8.3)**	**1 (8.3)**	**1 (8.3)**	**1 (16.7)**	**6 (16.7)**
Investigations	**1 (8.3)**	**2 (16.7)**	**3 (25.0)**	**-**	**-**	**-**	**-**	**-**	**-**	**3 (8.3)**
Blood creatine phosphokinase increased	1 (8.3)	1 (8.3)	2 (16.7)	-	-	-	-	-	-	2 (5.6)
Blood triglycerides increased	-	1 (8.3)	1 (8.3)	-	-	-	-	-	-	1 (2.8)
Renal and urinary disorders	**1 (8.3)**	**1 (8.3)**	**2 (16.7)**	**-**	**-**	**-**	**-**	**-**	**-**	**2 (5.6)**
Haematuria	1 (8.3)	1 (8.3)	2 (16.7)	-	-	-	-	-	-	2 (5.6)
Blood and lymphatic system disorders	**-**	**1 (8.3)**	**1 (8.3)**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (2.8)**
Anaemia	-	1 (8.3)	1 (8.3)	-	-	-	-	-	-	1 (2.8)
General disorders and administration site conditions	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (8.3)**	**1 (8.3)**	**1 (2.8)**
Pyrexia	-	-	-	-	-	-	-	1 (8.3)	1 (8.3)	1 (2.8)
Metabolism and nutrition disorders	**-**	**1 (8.3)**	**1 (8.3)**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (2.8)**
Hypernatraemia	-	1 (8.3)	1 (8.3)	-	-	-	-	-	-	1 (2.8)
Musculoskeletal and connective tissue disorders	**-**	**-**	**-**	**1 (8.3)**	**-**	**1 (8.3)**	**-**	**-**	**-**	**1 (2.8)**
Back pain	-	-	-	1 (8.3)	-	1 (8.3)	-	-	-	1 (2.8)
Respiratory, thoracic and mediastinal disorders	**-**	**-**	**-**	**-**	**-**	**-**	**1 (8.3)**	**-**	**1 (8.3)**	**1 (2.8)**
Rhinitis allergic	-	-	-	-	-	-	1 (8.3)	-	1 (8.3)	1 (2.8)

[a] System organ class and preferred term according to MedDRA (ver. 18.0).
[b] Total sum of subjects can be less than that of events when a subject experienced more than one adverse event after administrations of different study drugs (e.g., 2E05 experienced more than one adverse event in both the 1st (T20) and 2nd period (R20)

500 mg: R05: single administration of EC-18 500 mg 1 capsule under fasting conditions; T05: single administration of EC-18 500 mg 1 capsule after high-fat meal.

1000 mg: R10: single administration of EC-18 500 mg 2 capsules under fasting conditions; T10: single administration of EC-18 500 mg 2 capsules after high-fat meal.

2000 mg: R20: single administration of EC-18 500 mg 4 capsules under fasting conditions; T20: single administration of EC-18 500 mg 4 capsules after high-fat meal.

A total of 10 types of adverse events were identified in 6 subjects (16% of total 36 subjects). There were no significant differences among the subjects in the clinical study. All adverse events were considered to be unrelated to the study drugs. One case was identified as adverse event (1B02: Back pain) other than the moderate cases, all other cases were mild. A case of a moderate severity adverse event occurred after dosing two capsules of EC-18 500mg with a high fat diet, and was resolved after topical administration of ketoprofen. There were no significant adverse events or serious adverse events, and there were no clinically significant abnormal findings in clinical laboratory tests, vital signs, and ECG results.

10.3. Study Title: A Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral Administration of EC-18 in Healthy Subjects

A summary of adverse events from this study is provided in Table 6.

Table 6: Summary of Adverse Events

System Organ Class Preferred Term	EC-18 Dose Group					
	500 mg	1000 mg	2000 mg	4000 mg	Placebo	Overall
Number of Subjects	6.	6.	6.	7.	8.	33.
Any Treatment-Emergent Event	**0.**	**3 (50%)**	**0.**	**4 (57.1%)**	**1 (12.5%)**	**8 (24.2%)**
Nervous system disorders	0.	3 (50%)	0.	0.	1 (12.5%)	4 (12.1%)
Headache	0.	3 (50%)	0.	0.	1 (12.5%)	4 (12.1%)
Dizziness	0.	0.	0.	0.	1 (12.5%)	1 (3.0%)
Gastrointestinal disorders	0.	1 (16.7%)	0.	2 (28.6%)	0.	3 (9.1%)
Nausea	0.	0.	0.	2 (28.6%)	0.	2 (6.1%)
Vomiting	0.	1 (16.7%)	0.	1 (14.3%)	0.	2 (6.1%)
Infections and infestations	0.	0.	0.	1 (14.3%)	0.	1 (3.0%)
Urinary tract infection	0.	0.	0.	1 (14.3%)	0.	1 (3.0%)
Investigations	0.	0.	0.	1 (14.3%)	0.	1 (3.0%)
Blood pressure increased	0.	0.	0.	1 (14.3%)	0.	1 (3.0%)

Percentages were calculated using the number of subjects in the safety population for each dosing group as the denominator (n/N*100). Adverse events were classified as treatment-emergent if the adverse event had an onset date greater than or equal to the first dose date of study drug or if an event that occurred prior to first dose of study drug worsened during study treatment. Adverse events with a missing start date were considered treatment-emergent; missing start date was imputed as the first date of study treatment. A subject who reported the same system organ class or preferred term more than once was counted only once for that system organ class or preferred term.
Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities, Version 18.0.

One or more TEAEs were reported in eight (24.2%) subjects and none of them were serious or severe. The frequency of adverse events was relatively frequent in EC-18 1000 mg and 4000 mg treated groups (50.0% and 57.1%, respectively) when compared with the placebo, 500 mg or 2000 mg groups (12.5%, 0%, 0%). Four or more adverse events of dizziness, headache, blood pressure increased, and nausea were assessed as "possibly related" in their causality with the study drug. The maximum severity was grade 1 in 5 subjects (15.2%) and grade 2 in 3 subjects (9.1%). Subject 055 in the EC-18 4000 mg group of 055 stopped taking the study drug administration due to grade 2 vomiting after the first dosing. However, it was confirmed that there was a grade 2 headache before the administration of the test drug and the adverse event that occurred after the first dosing was resolved on the day of the onset. The investigator assessed that there was no causal relationship between the subject's adverse event and the study drug.

10.4. Summary

To date, clinical study results have shown that EC-18 is safe and tolerable for healthy volunteers at doses of 500 to 4000mg once daily or repeatedly for 14 days.

Rapid elevation of transient hepatic enzyme levels was observed in the single dose 2000mg group, but the subject recovered without developing any accompanying symptoms. In repeated

dose studies also, all TEAEs were mild and clinically significant changes were not detected in any of the subjects.

In healthy subjects, administration of EC-18 up to 2000mg with high-fat diets was safe and well tolerated, even though C_{max} and AUC systemic exposures were increased by up to 10 times. All TEAEs were mild to moderate in severity and causality was not confirmed and also no significant TEAEs occurred. Clinical laboratory tests, electrocardiograms, and vital signs also showed no clinically significant abnormal lab values or change patterns.

11. VIOLATION OF PROTOCOL, TERMINATION/WITHDRAWAL CRITERIA AND TERMINATION OF CLINICAL STUDY

11.1. Violation of Protocol

If it is discovered that a violation of the protocol has occurred during the course of the clinical study, the investigator should notify the monitoring staff of the violation as soon as possible and determine whether the applicable subject will continue to participate in the study. If a subject is withdrawn from the study due to a violation of the protocol, details of the incident should be recorded in the case report form. The following are considered serious violations of the protocol.

- If there is a breach of selection criteria and exclusion criteria that may affect efficacy and safety evaluation.
- If contraindicated concomitant drugs/treatments were used in combination during the study period.
- Any other violation considered to be a serious violation of the protocol.

11.2. Suspension and Withdrawal Criteria

Subjects who were administered with the study drug but for whatever reason cannot participate in the entire period of the study are classified as "withdrawals", including subjects who withdraw because of disease progression.

The subject may be withdrawn at any time if requested by a subject or the investigator determines that the subject should be discontinued.

The following are reasons for withdrawal of individual subjects:

- Withdrawal of consent by a subject or a subject's representative
- If it is difficult to continue in the study due to an adverse event
- If any violation of selection criteria or exclusion criteria is discovered during the course of the clinical study
- If contraindicated concomitant drugs were administered or it is determined that administration of contraindicated concomitant drugs is necessary.
- If it is impossible to do follow-up observation of a subject.

- If the investigator decides that it is difficult for a subject to continue the study for any other reasons

To follow-up on potential adverse events, subjects who are non-compliant with the visit schedule should be contacted directly by using all possible means. Reasons for withdrawal should be recorded in the electronic case report form (eCRF). The final end of study assessments should also be performed if possible. Subjects who withdraw from the study cannot re-enrolled in this study.

The sponsor may terminate the entire clinical study or the clinical study at a particular study center. The following are reasons for suspending the clinical study by the sponsor:

- Failure to enroll a targeted number of subjects.
- If there is efficacy/safety information that may significantly affect the continuation of the study.
- If the extent of violation of a GCP, protocol, or contract by a study center or an investigator is such that it poses problems in continuing the study.
- Other administrative reasons that may significantly affect the continuation of the study.

12. ENDPOINTS, EVALUATION CRITERIA AND EVALUATION METHODS

12.1. Efficacy Endpoints

12.1.1. Primary efficacy endpoint

Duration of restoration to ANC $\geq 1.5 \times 10^9$/L within the first 15 days

12.1.2. Secondary efficacy endpoint

The secondary efficacy endpoints include the following:

- Frequency of Grade 3-4 neutropenia (according to NCI CTCAE 4.03 version)
- Incidence rate of febrile neutropenia (according to NCI CTCAE 4.03 version)
- Time to reach the lowest point of ANC and time to be restored to Grade 2 or lower neutropenia
- Intravenous antibiotic dose rate and hospitalization rate
- The case in which infection-related adverse events high-risk or malignant clinical outcomes are expected and interventional therapy with fast-acting granulocyte colony stimulating factor is required (according to the recommendation by the 2015 ASCO clinical practice guideline update)

12.2. Method of Evaluating Efficacy

12.2.1. Neutropenia, Absolute Neutrophil Count (ANC), and Febrile Neutropenia

For 15 days after starting chemotherapy (except Days 3 and 4) the CBC is performed and the ANC is assessed daily or more frequently if it is determined to be clinically necessary for the safety of the subject (See Section 12.4.7). The grade for Neutropenia is assessed according to NCI CTCAE 4.03 version. Febrile neutropenia is assessed by ANC and body temperature according to NCI CTCAE version 4.03. Refer to the NCI CTCAE definition for neutropenia and febrile neutropenia.

12.2.2. Use of granulocyte colony stimulating factor (G-CSF)

Concomitant use of fast-acting G-CSF should be collected at each visit and record in the eCRF.

12.3. Safety Endpoints

- All TEAEs, SAEs, and incidence rate of TEAEs and SAEs that resulted in discontinuation of treatment.
- Laboratory test (hematological test, blood chemistry test, coagulation test and urine test result analysis) -- absolute values and changes from the baseline
- Vital Signs, weight, and 12-lead ECG -- absolute values and changes from the baseline

12.4. Method of Evaluating Safety

This study evaluates the safety of study drugs according to the results of physical examination, vital signs, electrocardiogram, laboratory tests (hematology, serum chemistry, coagulation test, and urinalysis), and adverse events. If necessary, additional safety tests may be performed as decided by the investigator, the sponsor, or the medical monitor of the study.

12.4.1. Adverse Events

All TEAEs from the date of signed consent to the final safety follow-up visit are collected during the entire period of the study. The definitions, collection, recording and reporting of TEAEs are described in Section 13.2.

12.4.2. Medical History

The history of each subject is collected at the screening visit and recorded on the corresponding page of the eCRF.

12.4.3. Physical Exam

The subject's weight is recorded at the Screening visit and Days 1, 8, 15, 22, and 50 visits. The height of the subject is recorded only at the screening visit.

During screening and safety follow-up visits (Days 22 and 50), physical exams are performed for all items (overall appearance, head, eyes, ears, nose, throat, neck, cardiovascular system,

pulmonary system, abdomen, breasts, lymph nodes, limb, nervous system, skin, and musculoskeletal system).

For other scheduled visits physical exams are performed for the following items only; General appearance, cardiovascular system, pulmonary system, abdominal, breast, lymph node, and other areas/system necessary to evaluate for adverse events.

During unscheduled visits, a physical examination is to be performed selectively at the discretion of the investigator.'

12.4.4. Vital Signs

Vital signs include oral temperature, blood pressure (systolic and diastolic), heart rate, and respiratory rate. Vital signs are assessed at key visits (screening and Days 1, 8, 15, 22, 50) and three consecutive measurements are taken with an automatic measurement device (at least every 2 minutes). Let the subject sit in a relaxed state for at least 5 minutes before taking vital signs. The study team should be careful in choosing an appropriate size of the blood pressure cuff for each subject. Oral temperature is measured by inserting a thermometer deeply underneath the tongue if possible, not just behind the teeth. Oral temperature should not be taken within 15 minutes after ingestion of food or drink.

12.4.5. Concomitant Medication / Treatment

During the entire study period, all concomitant medications and treatments are recorded in the concomitant medication section of the eCRF and reviewed by the investigator. Concomitant medications should be reviewed at all visits.

12.4.6. Electrocardiogram

A standard 12-lead ECG test is recorded two times before dosing (screening and Day 1) and two times after dosing (Days 22 and 50). Electrocardiograms are evaluated by an investigator or a qualified staff from the study team at a research institution. During unscheduled visits, assessment will be performed selectively at the discretion of the investigator. The electrocardiogram is interpreted and signed and dated by the investigator or the staff in charge. Electrocardiograms are classified into normal, abnormal but not clinically significant, or abnormal, clinically significant. In addition, the automatically calculated heart rate, PR interval, QRS interval, and QT interval (both Fridericia corrected and non-corrected values) and the findings and readings of the investigator are recorded in the eCRF.

Before starting the first cycle of chemotherapy, the investigator will evaluate the possibility of cardiac dysfunction in each subject through medical history, previous accumulation of anthracycline, left ventricular ejection fraction (LVEF) measured by echocardiography or MUGA (MUlti Gated Acquisition).

12.4.7. Clinical Laboratory Tests

Clinical laboratory tests include serum chemistry, hematology, coagulation, urinalysis, pregnancy, and serology. With respect to significant abnormalities in laboratory test results, repeat tests may perform for confirmation if it is deemed to be clinically necessary. Additional

monitoring and evaluation may be added if necessary to monitor the progress of the adverse event during the study period, to identify the cause of the abnormal outcome and to determine its significance.

Hematology; CBC and differential and platelet counts should be checked at screening visits and at the end of the dose and at Day 50. If the screening visit test is performed within one week from Day 1, the same test on Day 1 may be omitted.

CBC parameters include hemoglobin, hematocrit, RBC count, WBC count, platelet count, WBC differential count (absolute number and percentage of basophils, eosinophils, lymphocytes, monocytes and neutrophils), mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration and mean cell volume.

Serum chemistry panels and clotting panels are conducted at major visits (screening and Day 1, 15, 22, and 50). If the subject's screening visit test is performed within one week from Day 1, the same test on Day 1 may be omitted.

Clinical chemical parameters include electrolytes (sodium, potassium, chloride, and bicarbonate), calcium, phosphorus, blood urea nitrogen, creatinine, total protein, albumin, ALT, total bilirubin, glucose, uric acid, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and thyroid stimulating hormone. Subjects must be in a fasted state prior to collection of samples for clinical laboratory evaluations; thus, sample collection should occur before subjects have breakfast and administer study drug.

The coagulation parameters include the prothrombin time and the activated partial thromboplastin time.

The urinalysis is performed at the screening visit and Day 50 visit. Parameters include pH, specific gravity, protein, glucose, bilirubin or europilinogen, blood, nitrite, and white blood cell esterase. If abnormalities are observed with protein, blood, nitrite and/or leukocyte esterase, a microscopic examination is performed.

At the screening visit, the subject's serum for the presence of antibodies against HIV, hepatitis B virus, and C virus infection are screened.

At screening visits, urine hCG pregnancy tests are performed on all female subjects.

Also, on Day 1, 22, and 50, a urine pregnancy test will be performed on female subjects who have child bearing potential. If the subject's screening visit test is performed within one week from Day 1, the same test on Day 1 may be omitted.

13. ADVERSE EVENTS

This section defines the types of TEAEs and describes procedures for properly collecting, classifying, recording, and reporting AEs. The information in this section is in accordance with Federal Regulations (CFR) Part 312, ICH Guidelines E2: Clinical safety data management: Definitions and criteria of rapid reporting, and ICH guidelines E-6: In compliance with GCP.

Adverse events are recorded throughout the study and at the end of the study and are coded using the MedDRA which is the medical coding dictionary for regulatory affairs.

The principal investigator or qualified designee is responsible for detecting and documenting TEAEs regardless of whether there is a suspected causal relationship with treatment. For all TEAEs, the investigator must identify and seek out the information needed to determine the outcome of the TEAE and to assess whether the TEAE meets any of the SAE criteria that require prompt notice to the sponsor or designated representative.

13.1. Definition of Adverse Events and Their Attributes

13.1.1. Adverse Events

Adverse events are defined as any unintended or undesirable medical occurrences associated with the subject's participation in the study, regardless of whether or not they are considered to be relevant to the subject's participation in the study (ICH E6 Guideline for GCP) All medical conditions present at the screening of the subject are considered medical history and are not recorded as adverse events. However, if the condition worsens at any time during the study period, it should be recorded and reported as a TEAE.

13.1.2. Serious Adverse Events

The adverse event is considered "serious" if the investigator or the sponsor determines that it has resulted in any of the following:

- Death: Any deaths that occur during the study or during the follow-up period as specified in the protocol should be reported to the sponsor regardless of whether they are related to the treatment.
- Life-threatening events: An adverse event or suspected adverse event is considered a "life-threatening" response if the subject is considered to be at immediate risk of death due to the occurrence of the event in the opinion of the investigator or the sponsor. It does not include any adverse events or suspected adverse events that may have resulted in death in more severe forms.
- Hospital admission or extension of existing hospital stay
- Persistent or significant disability or significant impairment of one’s ability to perform normal function of life.
- An important medical event may be considered a serious adverse event if while it does not result in death, threats to life or hospitalization, based upon appropriate medical judgment, it may endanger the subject or may require medical or surgical intervention to prevent one of the above outcomes. Examples of such medical events include allergic bronchospasm requiring intensive care in the emergency room or at home, spasms that do not require blood disease or admission to hospital, or the occurrence of dependency or abuse of clinical trial medicines.
- Congenital birth defects or abnormalities

If any of the above definitions are met, regardless of their relevance to the severity or study drug, the response should be reported to the sponsor as described in Section 13.2.

Adverse events reported in clinical trials involving hospitalization or extension of hospital stay are considered serious adverse events. All hospitalizations meet these criteria. Admission includes transfer to an acute/intensive care unit in the hospital (e.g, from an internal medicine ward to an intensive care unit).

Hospital admission does not include the following:

- Rehabilitation facilities, hospice facilities or temporary care facilities (e. g, Guardian respite)
- Nursing homes or specialized nursing homes
- Emergency room visit
- Same-day surgery (Procedure that can be performed on the same day/transferred as an outpatient)
- Less than 24 hours visit for observation or evaluation that does not require hospitalization

Hospital stay or extension of hospitalization or hospital stay without cause or clinical adverse event is not an SAE. Examples include the following:

- Admission to treat an existing condition that has not been worsened
- Admission specified in the protocol (e.g., Procedures required in the protocol)
- Hospital admission for elective cosmetic surgery, or admission for social and/or convenience
- Pre-planned treatment or surgical procedures should be recorded in the baseline documentation for individual subjects.
- Diagnostic and surgical procedures should not be reported as TEAEs. However, if a medical condition occurred for which a procedure occurs performed during the reporting period and it meets the definition of an adverse event, it should be reported. For example, acute appendicitis that started during an adverse events reporting period should be reported as an adverse event.

13.1.3. Adverse Drug Reaction and Suspected Adverse Events

Drug adverse reactions are all adverse reactions caused by drugs. A suspected adverse event refers to any adverse event that has a reasonable likelihood that the drug has caused the adverse event. For safety reporting purposes, "reasonable likelihood" means that there is evidence suggesting a causal relationship between a drug and adverse events. Suspected adverse events refer to less certainty about the causal relationship than adverse drug reactions.

13.1.4. Unexpected Adverse Events

The sponsor is responsible for evaluating the expectedness of an adverse event. With respect to reporting to public health authorities, if the nature (severity), severity or incidence of an adverse event does not correspond to the product information described in the safety information provided in the Protocol/ Product Manual/Investigator Brochure/Prescribing Information for

EC-18, the adverse event is considered an "unexpected" adverse event. As used in this definition, "unexpected" refers to the occurrence of an adverse event or a symptom that is expected based on a class of drugs, or is expected based on the pharmacological properties of the investigation product. Unexpected adverse events based on a drug class may be included in the IB, but may not have resulted with the use of the investigational product under study.

13.1.5. Severity of Adverse Events and Serious Adverse Events

The study center should assess the severity of any AE experienced by subjects according to the criteria described in NCI CTCAE, Version 4.03, which describes the severity of the adverse events, analyzes and interprets the data, and provides a common term to describe clinical significance. Refer to the NCI CTCAE manual for specific events and grades of particular events of interest.

For events not listed in the NCI CTCAE Manual, use the following criteria in the NCI CTCAE Manual:

- Grade 1 = mild; Asymptomatic or mild symptoms; Clinical or diagnostic observation only; Intervention is not required
- Grade 2 = moderate; Minimal, local, or non-invasive intervention required; Age-appropriate use of tools in everyday life (e.g., meal preparation, shopping for groceries or clothes, phone use, money management, etc.)
- Grade 3 = Serious or medically serious severity but not immediately life threatening. Hospitalization or extension of hospitalization is required. Disability, and limited ability to perform self-care activities in everyday life (e.g. Bathing, putting on and taking off clothes, eating by yourself, using the bathroom, taking medicine. No bed rest related restriction.
- Grade 4 = life-threatening result. Emergency intervention is required.
- Grade 5 = death associated with AE

Additional information and a printed version of the NCI CTCAE manual are available at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Note: Serious and severe are not synonymous. The criteria for “serious” defined above serve as a guide for defining the obligations of regulatory reporting. The term severity is usually used to describe the intensity (severity) of a particular event (e.g., mild, moderate or severe headache). However, the event itself may have relatively minor medical significance. This is not the same as severity based on the subject/harmful outcome. Thus, while severe headache TEAE may not be considered significant, a moderate-severe infection that causes the subject to be hospitalized should be reported as SAE.

13.1.6. Relationship Between Adverse Events, Serious Adverse Events and Administration of Study Drugs

The investigator must record his or her opinion on the relationship of study drug therapy with TEAE in AE eCRF. The causal assessment of the investigator is to determine whether there is a

reasonable possibility that the study drug has caused or contributed to an AE and the assessment should be carried out on all TEAEs.

The sponsor's determination on causality is used for appropriate health authority reporting. The relationship of a TEAE to participation in the study is determined by using the descriptions and definitions provided in the table below.

Not applicable (Unrelated)	There is no relationship with the study drug in terms of time or there is a valid causal relationship between TEAE and other drugs, concomitant diseases or environment. TEAE is definitely not related to the study drug.
Not related (Unlikely)	Although there is a temporal relationship to the study drug, there is no valid causal relationship between the study drug and TEAE. It is suspected that there is an association between AE and the study drug.
It is possibly related. (Possibly)	There is a valid causal relationship between the study drug and TEAE. TEAE may be associated with the study drug.
A relationship exists. (Related)	There is a reasonable possibility that TEAE was caused by the study drug. The expression "reasonable likelihood" generally means that there are facts (evidence) or claims that represent a causal relationship (21 CFR 312.32 (a)). There is a relationship between TEAE and the study drug.

13.2. Collection and Recording of Adverse Events and Serious Adverse Events

All TEAEs and SAEs from the subject consent form to the last follow-up (Day 50) are recorded in the appropriate eCRF page. The investigator must specify the following information in the eCRF for each TEAE:

- TEAE must be described by using accurate medical terms. To avoid vague, ambiguous, or colloquial expressions, TEAE should be recorded in standard medical terms, not expressions used by the subject. If possible, a diagnosis should be provided if the signs and symptoms are common etiology (e.g. Cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").
- Start date
- End date
- The degree of severity (i.e., level) assessed by the investigator according to the definition of NCI CTCAE, Version 4.03,
- Causal relationship with the study drug evaluated by the investigator. The crucial factor in the document is the slight relationship between time and the adverse event.
- Measures taken (e.g. None, administration concomitant medication, new hospitalization or extension of hospital stay, procedure)
- Outcome (e.g. Disappeared, disappearance with sequelae, progress)
- Seriousness status of TEAE
- Discontinuation of taking the study drug or withdrawal from the study by the subject due to TEAE

If the same TEAE occurs multiple times in one subject (unless the AE is persistent and stable), the AE under investigation is documented and evaluated at each occurrence.

If an electronic data collection (EDC) system cannot be accessed and an SAE occurs, a written SAE reporting form can be completed and faxed to the sponsor or designated person.

Serious adverse events are recorded in the AE eCRF form and reported to the health authorities if applicable.

If pregnancy occurs, it should be recorded on the eCRF form and reported. Pregnancy itself is not considered an AE unless there is suspicion that the study drug may interfere with the effectiveness of the contraceptive medication. All pregnancy outcomes (natural miscarriage, selective abortion, normal delivery or congenital anomalies) should be followed up and documented even if the subject has stopped participating in the study.

All reports of congenital defects/abnormalities are SAEs. A natural miscarriage should also be reported and processed as an SAE. Selective abortion without complications should not be treated as a TEAE.

13.2.1. Collection Period

All TEAEs are collected from the time of consent of the subjects to the last follow-up observation. All TEAEs should be treated and followed up as medically appropriate until recovery, stabilization, or the subject is lost-to-follow-up.

13.2.2. Collection Method

TEAEs can be collected as follows:

- Observation of the subject
- Ask unbiased and non-leading questions to the subject
- Receiving voluntary complaints from the subject

Abnormal values or outcomes from clinical or laboratory evaluations may indicate AE if judged to be clinically significant by the investigator. In this case, the results should be recorded as AE in the supporting document and in the appropriate AE form. The assessment that produced the value or result should be repeated until the value or result is returned to normal or stabilized and the safety of the subject is not compromised.

13.2.3. Reporting of Serious Adverse Events

The following procedures for SAE reporting should comply with 21 CFR 312 and the ICH Guidelines. After becoming aware that the subject has experienced SAE, the investigator or a designated person is responsible for reporting the SAE to the safety of the ARG within 24 hours of the event, regardless of its relevance to the study drug or expectedness. The initial SAE report should contain as much information as possible, but at least should include the following:

- Reporting person
- Subject ID number
- Serious adverse event terms
- Relationship between the study drug and the event

- Reason for the event's significance

At the time of SAE reporting, a supplementary eCRF page should be present: If applicable, medical history, concomitant medication, demographic information and administration of the study drug

Reporting of known information should not be delayed because of unlikely details about the incident. Once additional details become available, the SAE eCRF page must be updated and resubmitted through the EDC system.

For additional information on SAE reporting, contact ARG safety:

Safety Report Contact:

ARG Safety Fax: 1-866-851-9318

ARG Safety E-mail: safety@atlanticresearchgroup.com

ARG Safety Phone: 1-888-619-3216

Report serious adverse events to public health authorities

The sponsor submits an application for approval of protocol (Investigational New Drug, IND) safety report to the US Food and Drug Administration (FDA) in accordance with the FDA regulations detailed in 21 CFR 312.32.

In other countries, serious adverse events are reported promptly to the relevant licensing authorities in accordance with national requirements.

Reporting serious adverse events to Institutional Review Board health authorities

It is the responsibility of the investigator to promptly report to the respective IRB or IEC any other issues involving risks to the subject as mandated by the IND Safety Report or the IRB/IEC.

13.3. Follow-up of Adverse Events

The investigator should appropriately treat subjects who have experienced TEAEs and SAEs and observe at appropriate intervals until the AE's resolution or stabilization of the condition (based on the time of earlier occurrence). If a certain drug is administered in response to a TEAE, the drug should be recorded as a concomitant drug in the concomitant drug eCRF page. Measures taken and results should also be recorded. The investigator should follow-up with the subject until resolution or stabilization of the TEAE/SAE. This follow-up information should be recorded in the eCRF.

14. PREGNANCY

Women of childbearing age should use appropriate contraception during the study period. The appropriate methods of contraception to be accepted in this study are as the following:

- Hormonal contraceptive
- Implantation of intrauterine devices or intrauterine systems
- Blocking method (Spermicide and condom / spermicide and intravenous diaphragm, vaginal sponge or neck cap)
- Infertility treatment (partner's vasectomy, bilateral tubal ligation)

The investigator is responsible for reporting and following up on the subject's pregnancy that has occurred during the clinical study period. Pregnancy itself is not considered an adverse event if the pregnancy is not relevant to the study drug.

Within 24 hours after the pregnancy is known, the investigator prepares an initial pregnancy report and reports it to the sponsor. The investigator must carry out follow-up investigations and document all pregnancy processes and results, even if the subject withdraws consent or terminates the study. In addition, the investigator should prepare a pregnancy outcome report and submit it to the sponsor within 24 hours after the result of all pregnancy is known.

All serious adverse events that occur during pregnancy should be recorded in the AE eCRF immediately in accordance with the procedure.

14.1. Reporting of Pregnancy

If any subjects are suspected of pregnancy during the study period (e.g., absence or delay of menstruation) they should be instructed to contact the investigator immediately. If pregnancy is confirmed, the subject will stop the study and followed up until the end of the pregnancy.

Although pregnancy is not considered an AE, the investigator is responsible for reporting all possible pregnancy information through eCRF within 24 hours after becoming aware of the incident. The investigator should discuss with the subject and discuss the possible risks to the fetus and the risk of continuing pregnancy. The subject should be referred to an obstetrician/gynecologist who has experience in reproductive toxicity for further investigation and counseling. The subject should be monitored continuously until the end of the pregnancy. Once data become available, detailed follow-up information on pregnancy outcomes and the health of the newborn should be reported.

All pregnancy complications or early termination, including abortion, miscarriage, or spontaneous termination of pregnancy for medical reasons, must be reported as an SAE. If the pregnancy has caused congenital birth defects or abnormalities, a separate SAE report must be recorded in the eCRF. In addition, all neonatal deaths occurring within 30 days of birth should be reported as SAE, regardless of causality. Furthermore, the investigator should also report infant death following a 30-day reporting period that is suspected of being associated with intrauterine exposure to the study drug.

15. STATISTICS

15.1. Determination of Sample Size

The scope of the study is based on a minimum number of subjects required to assess basic feasibility and to assess overall safety, tolerability, and efficacy of the study drug on hematological and immunological parameters. Following the 3 + 3 dose escalation design, four cohorts of three persons each will be recruited. If a DLT occurs at a dose, three additional subjects will be recruited for the dose cohort in which the DLT occurred.

15.2. Target Groups

Efficacy assessment is done through full analysis set (FAS) defined as subjects who received one or more doses of a study drug, and had at least one baseline efficacy assessment. Safety assessment is done through safety set, defined as subjects who have received at least one dose of study drug.

15.3. Statistical Analysis

This study assesses the safety and tolerability of the study drug as assessed by physical examination, vital signs, laboratory tests, ECG and TEAE evaluations. Descriptive statistics (mean, median, maximum, minimum and standard deviation) from the quantitative safety data and, if applicable, the baseline are calculated. Qualitative safety data are categorized using frequency.

- Adverse events are coded by using MedDRA and grades are assigned based on NCI CTCAE, Version 4.03. The number and percentage of subjects who reported TEAE at least once are tabulated using the worst CTCAE grade, somatic system classification and recommended terms. Similarly, the SAE and TEAE that resulted in the discontinuation of the study drug are summarized separately.
- The number and percentage of subjects who experienced grade 3 or 4 neutropenia, grade 3 or grade 4 febrile neutropenia and/or grade 3-4 grade thrombocytopenia (see NCI CTCAE Version 4.03) are summarized by treatment group and 95% confidence interval for ratio is also presented.
- The time it takes for neutropenia to recover is defined as the time until Grade 3 or 4 neutropenia recovers to grade 2 or lower. Subjects who have not reached the target ANC level will be withdrawn early on the last laboratory assessment date. Estimate the Kaplan-Meier survival rate and calculate the 95% confidence interval for the median value. The results will be summarized in graph and table form.
- Descriptive statistics are provided for the lowest level of ANC during treatment periods for each treatment group.
- The number and percentage of subjects receiving G-CSF for treatment of neutropenia will be tabulated.
- Individual data for concomitant medications, medical history, and physical examination will be listed. Detailed analysis will be described in the statistical analysis plan.

16. DIRECT ACCESS TO SUPPORTING DATA/DOCUMENTS

16.1. Study Monitoring

In accordance with the ICH GCP Guidelines, the sponsor of this study is responsible for ensuring proper enforcement of the protocol and the validity of the data recorded in the eCRF in relation to proper implementation of the study. The Clinical Research Organization (CRO) is responsible for assigning study monitor personnel for this study. The responsibility of the study monitor is to support investigators and CROs in their effort to maintain complete, accurate, readable, well organized, and easily recoverable data. The test monitor personnel will advise investigators on the regulatory needs for monitoring, checking, IRB/IEC reviews and surveys related to the study by directly viewing the supporting data/documentation. In addition, study monitor personnel will explain and interpret to the investigator all the rules applicable to the clinical evaluation of the study drug as documented in the ICH Guidelines.

It is the responsibility of the test monitor personnel to check the eCRF and supporting documentation to ensure that the subject's rights are protected throughout the study, compliance with the protocol, the completeness, accuracy and consistency of the data, and that the study has been performed in compliance with local regulations.

16.2. Supporting Documentation

The CRO and Enzychem Lifesciences Corporation require that investigators prepare and maintain adequate and accurate records of each subject receiving the study drug. Supporting documents, such as all hospital, clinic or exam room charts and signed informed consent forms, will be included in the investigator file along with the study record of the subject.

The study data are entered electronically. The study team at the study center will record eCRF data from supporting documents. If any data is first recorded in the same document as the experimental report, these documents are considered as supporting documents.

16.3. Data Collection and Management

This study will be conducted based on the "Industry Guideline - E6 Good clinical practice (GCP) Incorporation guideline." This study will also be carried out in accordance with the Helsinki Declaration (2013).

This study uses EDC (a technique of collecting data directly from a testing laboratory using eCRF). This data are stored in a well-validated clinical database that has been centrally and sufficiently validated. The investigator is responsible for ensuring that all parts of each eCRF are written promptly and accurately and that the inputs can be verified against all supporting data.

The study monitor personnel will carry out 100% verification of supporting documentation to ensure that there is no inconsistency between the eCRF and the supporting documentation. Discrepancies will be resolved in accordance with the principles of the GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan.

On a regular basis throughout the study period and upon completion, data will be sent to the SAS data set from the database.

Data management is coordinated by the CRO's Data Manager in accordance with standard operating procedure guidelines for data management and formal study data management plans.

17. QUALITY CONTROL AND QUALITY ASSURANCE

The quality assurance includes all planned systematic measures established to ensure that clinical studies are conducted in accordance with the ICH GCP and local/regional regulatory standards and that data are generated, documented (recorded) and reported.
Continuous monitoring and quality assurance of a separate CRO (or qualified representative) can be regularly assigned to investigate the actual status of clinical studies by reviewing secured data and procedural aspects. Such fact finding investigations may include factual investigations/inspections of the study center and verification of supporting documents. Direct viewing of supporting documentation is necessary for such periodic fact finding investigations/inspection purpose.

18. ETHICS

18.1. Ethics Review

Prior to providing the IRB/IEC approved evidence to the Enzychem Lifesciences Corporation and the contract research organization, the investigator will not start the study and the study drug will not be shipped to the study center. The investigator will quickly report to the IRB any changes to the research activity and any unexpected problems involving the risk to the subject. Except when it is necessary to remove the obvious immediate risk to the subject, the investigator will not make any changes to the study without obtaining approval from IRB/IEC approval. The investigator reports progress to IRB/IEC as required by IRB/IEC. The investigator will provide a final report to IRB after the study participation is completed.

18.2. Ethical Execution of the Study

The investigator should carry out the study according to the protocol, Helsinki declaration and ICH GCP guidelines. The investigator and Enzychem Lifesciences Corporation will sign a study contract and the protocol to confirm the agreement. The investigator will not make any amendment(s) without the consent of IRB/IEC of Enzychem Lifesciences and IRB/IEC through approval/information except when necessary to eliminate the immediate danger to the subject or when the change involves only the shipment or administrative aspects of the study and will not implement any revisions (deviation from or changes of the protocol).

18.3. Informed Consent Form

18.3.1. Subject Instructions and Informed Consent Form

The informed consent form is approved by the appropriate IRB/IEC for the study center. The provisions of 21 CFR 50.25 and the ICH GCP shall be applied to the informed consent form. The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information will be provided both verbally and in writing as much as possible. No subject is obligated to participate in the study. The subject or his/her relative, guardian or (if applicable) legal representative should be given sufficient opportunity to ask questions about the details of the study. The information should clearly state that declining to participate in the study or discontinuing the study at any stage will not incur any harm the subject's subsequent treatment. Subjects should be allowed sufficient time to decide whether to participate.

The subject should be aware and agree that the study monitor personnel, the inspector, the IRB/IEC and the regulatory authority will directly view the supporting medical records. The subject should be notified that such review does not infringe on the confidentiality of the subject’s information or possible provisions. The subject must also be informed that the subject acknowledges such viewing by signing the consent form. Each of the subjects is provided with a copy of the signed consent form to keep as their own records.

A copy of the sample informed consent form is provided in Attachment 1.

18.3.2. Subject Confidentiality

Medical information of each subject obtained as a result of this study is considered as confidential information and disclosure to third parties is prohibited. Access to the information is allowed to authorized parties or employees only. Medical information may be provided to the subject's study doctor or other appropriate medical staff responsible for the welfare of the subject. The investigator must fill out a form that allows each subject to notify the subject's primary care physician of the subject's participation in the study.

19. ADMINISTRATIVE PROCEDURE

19.1. Publication of the Clinical Study

The protocol and study results will be disclosed through www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c. The results and data obtained from this study will be reverted to Enzychem Lifesciences as its property.

19.2. Revision and Deviation of the Protocol

If the investigator and Enzychem Lifesciences Corporation agree not to change or modify the protocol after all the parties have agreed and signed it, the researcher and the investigator and Enzychem Lifesciences Corporation may not change or revise the protocol. Any changes should be recorded in writing and signed by the researcher and Enzychem Lifesciences Co., Ltd. in the change plan.

Unless immediate action is required for safety reasons (IRB/IEC are notified in case of immediate action), approval from the Institutional Review Board/ IEC must be obtained prior to implementing any change.

Except for the purpose of protecting the subject's life or physical well-being in an emergency situation, the protocol or the study plan may not be violated. Except for such an emergency situation, approval from the sponsor prior to violation of the planned protocol, regulatory authorities (E.g., FDA) or IRB/IEC if applicable. Any deviations from the protocol that occur during the study period should be documented and reported in accordance with the rules of Enzychem Lifesciences and, if applicable, the IRB/IEC. Additional details on documentation, evaluation and tracking of deviations from the protocol are described in detail in the monitoring plan of this study.

Exemptions are not approved for inclusion/exclusion criteria; in order for the subject to be registered, all criteria must be met exactly as specified. In addition, pre-planned deviation from the protocol or study plan is not permitted except to protect the subject's life or physical well-being in an emergency situation. Any deviation that is unintentional or occurs as a result of an action taken on the subject must be documented and reported in accordance with the provisions of Enzychem Lifesciences. And the IRB/IEC, if applicable. Additional details on documentation, evaluation and tracking of deviations from the protocol are described in detail in the monitoring plan of this study.

20. DATA HANDLING AND RECORD RETENTION

20.1. Survey of Records

Enzychem Lifesciences Co., the CRO, a designated person, IRB/IEC or regulatory authorities are allowed to monitor all aspects of the study or visit the study center’s facilities for the purpose of fact finding investigations. The investigator will agree to permit the inspection of the study drug storage area, study drug inventory, study drug record, subject chart and study supporting

document, and other record related to implementation of the study designated by the Enzychem Lifesciences, CRO, designated person, IRB/IEC or regulatory authorities.

20.2. Record Maintenance

The investigator should keep all documentation related to the study for at least two years after the last marketing authorization of the study drug, or two years after the study substances are discontinued unless the study drug is approved. If these requirements are different from local regulations, local regulations that do not have a record retention policy of less than two years shall prevail.

20.3. Maintenance of Samples

Samples can be used for the purposes related to this study. The sample can be kept until the study team determines that the sample is no longer needed and that no sample is required to be re-analyzed. In addition, the identifiable samples may be discarded at any time upon the subject's request.

21. SUBJECTS' CARE AND TREATMENT STANDARD AFTER THE CLINICAL STUDY

Subsequent care and treatment of subjects who have ended the clinical study early and those who have completed the study are subject to the criteria and principles of treatment for common target diseases.

22. MEASURES TO PROTECT THE SAFETY OF THE SUBJECT

22.1. Study Center

The chief of the study center should facilitate preparations so as to have appropriate space, facilities and professional manpower necessary for carrying out the clinical study step by step and properly carry out the clinical study.

22.2. Principal Investigator

The principal investigator should be thoroughly familiar with the adverse events and precautions specified in the protocol, and should immediately report any significant adverse events during the course of the study to the IRB and the sponsor.

22.3. Study Staff

The study staff should be well informed in advance regarding expected adverse events and usage precautions etc., and in the event that any serious adverse events occur while conducting the study, the staff should immediately report to the principal investigator and the sponsor.

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Protocol Agreement

Study Title	EC-18 for Management of Chemotherapy-Induced Neutropenia in Patients with Advanced Breast Cancer Receiving Low Febrile Neutropenia Risk Chemotherapy: Dose-escalation, Open-label, Multicentre Clinical Trial to Assess the Safety and Tolerability of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen
Protocol No.	EC-18-201

I have read and reviewed the protocol and I understand and agree that the protocol contains all the information necessary to carry out the clinical study. I will make reasonable efforts to complete this study within the planned time frame. I will conduct this clinical study in accordance with the Helsinki Declaration, the ICH-Good Clinical Practice (GCP) and all regulations of the applicable country.

Principal Investigator:

_____	_____	_____/____/_____
Printed Name	Signature	Date (DD-MMM-YYYY)

Sponsor:

_____	_____	_____/____/_____
Printed Name	Signature	Date (DD-MMM-YYYY)

Signature Page

Study Title	EC-18 for Management of Chemotherapy-Induced Neutropenia in Patients with Advanced Breast Cancer Receiving Low Febrile Neutropenia Risk Chemotherapy: Dose-escalation, Open-label, Multicentre Clinical Trial to Assess the Safety and Tolerability of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen
Protocol No.	EC-18-201
Effective Date	Date of signature by the final approver

C&R Research Inc.

Written by:

(Medical writer)	Signature	Date (DD-MMM-YYYY)
(Statistician)	Signature	Date (DD-MMM-YYYY)

Reviewed by:

(Medical Manager)	Signature	Date (DD-MMM-YYYY)
(Project Manager)	Signature	Date (DD-MMM-YYYY)

Sponsor Name

Approved by:

(Role)	Signature	Date (DD-MMM-YYYY)
(Role)	Signature	Date (DD-MMM-YYYY)

24. APPENDICES

Appendix 1: Doxorubicin Drug Information

Appendix 2: Cyclophosphamide Drug Information

Appendix 3: Nausea and Vomiting Management Guideline

Nausea Management Criteria		
CTCAE Grade	Symptoms	Recommendation
1.	Loss of appetite without alteration in diet	No action required. Continue dosing
2.	Decreased oral ingestion without clinically significant weight loss, dehydration, or malnutrition	Provide 5-HT3 antiemetic treatment. Provide fluid supplementation. Symptoms continuing ≥ 3 days (72 hours), may interrupt EC-18 until symptoms return to Grade 1
3.	When oral caloric or fluid intake is insufficient; tube feeding, total parenteral nutrition (TPN), or hospital admission is indicated	Provide 5-HT3 antiemetic treatment. Provide fluid supplementation. Grade 3 Symptoms for ≥ 3 days requires interrupting EC-18 until symptoms return to Grade 1. EC-18 interruption for more than 4 days requires patient discontinuation from study
Vomiting Management Guideline		
CTCAE Grade	Symptoms	Recommendations
1.	1 - 2 episodes (with at least 5 min interval) for 24 hours	• Provide 5-HT3 antiemetic treatment.
2.	3 - 5 episodes (with at least 5 min interval) for 24 hours	• Provide 5-HT3 antiemetic treatment. • Provide fluid supplementation. • Symptoms continuing ≥ 3 days (72 hours), may require interruption of EC-18 until symptoms return to Gr 1
3.	≥6 episodes (with at least 5 min interval) for 24 hours; tube feeding, total parenteral nutrition (TPN) or hospital admission is indicated	• Provide 5-HT3 antiemetic treatment. • Provide fluid supplementation. • EC-18 is to be suspended if Gr 3 symptoms continue ≥ 3 days. • If the Grade 3 symptom continues for ≥ 2 days and cannot be controlled with standard antiemetics, the subject must be withdrawn from study.
4.	Life-threatening symptoms considered treatment related	• Provide 5-HT3 antiemetic treatment. • Provide fluid supplementation. • Patient with DLT is removed from study

Standard Daily Doses of 5-HT3 Serotonin Inhibitor Antiemetic Agents

Daily dose of all antiemetic agents prescribed during antiemetic treatment should be recorded in the CRF along with starting and ending dates. See Table 2 below.

Antiemetic treatment should follow the recommendations provided through the declaration agreed by the Antiemetic Subcommittee of European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) [1, 2].

While prophylactic administration of antiemetic drug is not mandatorily recommended during a combination treatment of doxorubicin and cyclophosphamide, it may be a treatment option if clinically indicated. In this study, investigational product will be taken with food after Day 1 in which doxorubicin and doxorubicin are to be administered. Antiemetic agents may be administered prophylactically to all subjects according to the following recommended usage and dose based on the investigator's judgment within 3 days after the starting day of dosing, where vomiting can be induced by chemotherapy, for improving compliance and minimizing discomfort for subjects to achieve more accurate assessment on the safety and effectiveness of the investigational product. Subsequently, nausea and vomiting will be managed based on Table 1 and guidelines of this document and clinical judgment of the investigator to minimize discomfort for participating subjects and to enhance the reliability of the study results.

Table 2. Recommended doses of serotonin $(5\text{-HT})_3$ receptor antagonists

Agent	Route	Antiemetics
Ondansetron	IV	8 mg or 0.15 mg/kg
	Oral	16 mg[a]
Granisetron	IV	1 mg or 0.01 mg/kg
	Oral	2 mg (or 1 mg[b])
Dolasetron	Oral	100 mg
Tropisetron	IV	5 mg
	Oral	5 mg
Palonosetron	IV	0.25 mg
	Oral	0.5 mg

[a]Randomised studies have tested the 8 mg twice daily schedule.
[b]The 1 mg dose is preferred by some panellists.

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25. ATTACHMENTS

Attachment 1: Subject Instructions and Informed Consent Form

Clinical Study Subject Information Sheet

Study Title: Dose-Escalation, Open-label, Multicentre Clinical Trial to Assess the Safety, Tolerability of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen

Name of Site/Investigator:
Subject Identification Code (Screening No.):

Protocol No.: EC-18-201

This subject information sheet includes general information and descriptions about this study and study drug to provide you with information that can help you decide whether to participate in this study. If there is anything that you do not understand in this subject information sheet or you have additional questions about this clinical study, you can ask your study doctor and study staff provided in the last section of this subject information sheet.

You will be asked to voluntarily sign the Informed Consent Form (ICF) after listening to the explanations about the clinical study and taking sufficient amount of time to understand the information. If you agree and choose to participate, you can sign the attached ICF by hand. After signing it, you will receive 1 copy of the subject information sheet and signed ICF respectively.

1. What is the purpose of this clinical study?

This clinical study is being conducted for research purposes. Research means that the efficacy and safety of the study drug have not been completely confirmed at this point. The purpose of this clinical study is to confirm the safety at each dose of EC-18 in breast cancer patients and to evaluate the improvement and effects of neutropenia caused by cancer chemotherapy (chemotherapy).

In this clinical study, the optimal dose and safety of the study drug will be checked and the effects and safety of the treatment for neutropenia caused by cancer chemotherapy (chemotherapy) of the study drug will be confirmed as the exploratory purpose of this study.

2. What type of drug is being used in this clinical study?

The study drug, EC-18 is a substance that belongs to the chemical family of monoacetyl diacylglyceride (MDAGs) and is mainly found in deer antlers and also in natural state including mammary gland tissue of bovine and certain Ascomycota.
The EC-18 that you will be taking has been marketed with the approval by the Ministry of Food and Drug Safety at 2014 in Korea through a health functional food, Rockpid®, which aims to improve immune functions. This is a safe drug as there were no reported side effects despite 15,000 bottles or more sold in the market up to now. Furthermore, this product has been through the verification process that involves going through all toxicity tests recommended by the

Ministry of Food and Drug Safety, and the results did not show any side effects.
You will receive cytotoxic anticancer drug for treating breast cancer. This type of cancer chemotherapy (chemotherapy) generally causes mitochondrial damage and oxidation stress in normal cells and cancer cells and as a result, it causes cancer chemotherapy (chemotherapy)-induced neutropenia (decreased white blood cells). The EC-18 you will be taking is expected to prevent neutropenia or improve severe neutropenia during the course of receiving cancer chemotherapy (chemotherapy) by activating various factors or effectively decreasing manifestation in the body that are induced by chemotherapy to cause neutropenia
You will take EC-18 once a day after breakfast for 3 weeks during the entire clinical study period and you will receive it from the study doctor during the baseline visit (start of treatment).

3. How many subjects will participate in this study and what is the percentage of subjects assigned to each of the treatment groups?

- All registered subjects will receive EC-18. In this clinical study, about 12 subjects are expected to enroll in the study among the subjects who have completed the monitoring at Week 4 from receiving the study drug. 12 people will be divided into 4 small groups that consist of 3 persons and take 4 different doses to check which dose is most safe and effective. In order to do this, about 2mL of blood will be drawn from each of 11 blood draws to measure the drug concentration in the blood while being hospitalized on Day 1 and Day 15 of the study treatment. If a major adverse event related to the drug is confirmed, 3 additional subjects may be registered in addition to the existing 3 people.

4. How long is the participation period for this clinical study?

The screening period to determine the eligibility of participation in the study may be up to 4 weeks (28 days). Upon the final registration, your participation period is scheduled as approximately 7 weeks (50 days). However, confirmation procedures for the test result may be delayed. Also, side effects (adverse events) may occur and more time may be needed to treat side effects. Thus, the participation period may be prolonged or shortened than the scheduled period.

5. The process of this clinical study is as follows:

This clinical study is composed of a screening visit, baseline visit, and follow-up period.

- Screening visit: a visit and preparation period in order to determine eligible subjects for the study.

If you agree to participate in this study, you will be evaluated to see if you are suitable to participate in this study by implementing the below screening visit test/investigation. This process is called a screening test (screening) and only the subjects who satisfy the screening criteria will be able to participate in this clinical study. The screening test is expected to take about 1~2 hours. If it is determined that you are suitable to participate in this study after going through all of these preparation steps, you will receive the study drug once a day for 3 weeks starting from your next visit. Subsequently, safety will be confirmed through the follow-up period.

- Items of Examination/Investigation at Screening Visit

- ☐ Sign the Informed consent form
- ☐ Demographic information (gender, date of birth)
- ☐ Current or past medical history
- ☐ ECG test
- ☐ Heart function test (ultrasound or scan)
- ☐ Chest radiography
- ☐ Drug history
- ☐ Weight and height measurements
- ☐ Take measurement of temperature, blood pressure, heart rate, and respiratory rate
- ☐ Physical examination
- ☐ Assessment of ECOG performance status
- ☐ Assessment of the dose of previously received anti-cancer drug and heart function
- ☐ General blood test, serum chemistry test, blood coagulation test, virus serum test, and urine test
- ☐ Urine pregnancy test (only for women of child bearing potential): If positive (pregnant), she cannot participate in this study.

■ Baseline visit (Day 1): Administration of the study drug

If it has been determined that you are eligible for this study from the screening test, you will begin receiving the study drug according to the protocol. You will receive the study drug once a day for a total of 3 weeks and the first dose will be provided after breakfast at the baseline visit under the guidance of the study doctor. Starting from the following day, you must take the drug after having your breakfast and maintain a daily record to track if you have taken the drug, how many tablets you took, and whether you vomited after taking the drug.

The clinical study is divided into a total of 4 dose groups which are 500 mg, 1000 mg, 1500 mg, and 2000 mg, and you will be receiving a dose according to one of these dose groups.

The following items will be tested at the baseline visit, and it will take approximately 1 to 2 hours.

- ☐ Randomization (only for phase 2)
- ☐ ECG test*
- ☐ Take drug history
- ☐ Take measurement of body weight
- ☐ Measurements of body temperature, blood pressure, heart rate, and respiratory rate are taken
- ☐ Physical examination
- ☐ Assessment of ECOG performance status
- ☐ General blood test, serum chemistry test, and blood coagulation test*
- ☐ Reticulocyte test for the assessment of bone marrow function;
- ☐ Urine test
- ☐ Urine pregnancy test*
- ☐ Administration of chemotherapy

- Check for side effects

* To be administered if needed: It will be administered only if a 1 week or longer period has passed since the last visit.

■ Follow-up visit: Visit schedule after receiving the first study drug

Starting from the following day after you receive the first dose of the study drug (Day 2) up to Day 15, you must visit the hospital daily to take blood tests. In addition, you may need to make additional visits to the hospital after Day 15 if it is determined by your doctor that continuous tests are needed for side effects.

When you visit the hospital on Day 8, Day 15, Day 22, and Day 50, you will undergo more tests including ECG, ECOG performance status assessment, and chest radiography. On Day 8, Day 15, Day 22, and Day 50, an interview and physical examination is planned to assess any discomfort, side effects, and conditions during the study. Therefore, the tests you go through during each of your visit may vary.

Tests and procedures for each visit are as follows and tests that do not require hospitalization will take about 1~2 hours.

Tests scheduled at each visit are as follows:

1) Day 2-7 and Day 9-14
   - General blood test

2) Visit at Day 8
   - Drug history
   - Body weight measurement
   - Measurement of temperature, blood pressure, heart rate, and respiratory rate
   - Physical examination
   - General blood test, serum chemistry test, and blood coagulation test
   - Reticulocyte test for the assessment of bone marrow function;
   - Check for side effects

3) Visit at Day 15
   - Drug history
   - Body weight measurement
   - Measurement of temperature, blood pressure, heart rate, and respiratory rate
   - Physical examination
   - General blood test, serum chemistry test, and blood coagulation test
   - Check for side effects

4) Visit at Day 22
   - ECG test
   - Drug history
   - Body weight measurement
   - Measurement of temperature, blood pressure, heart rate, and respiratory rate

- Physical examination
- Assessment of ECOG performance status
- General blood test, serum chemistry test, blood coagulation test, and urine pregnancy test
- Reticulocyte test for the assessment of bone marrow function;
- Chest radiography (if needed)
- Check for side effects

5) Visit at Day 50 (last visit)
   - ECG test
   - Drug history
   - Body weight measurement
   - Measurement of temperature, blood pressure, heart rate, and respiratory rate
   - Physical examination
   - Assessment of ECOG performance status
   - General blood test, serum chemistry test, blood coagulation test, and urine test
   - Reticulocyte test for the assessment of bone marrow function;
   - Urine pregnancy test
   - Chest radiography
   - Check for side effects

If any side effects still remain at the last visit (Day 50) of this study, a telephone follow-up will be carried out to monitor the progression of the side effects, etc. You may visit the clinic after the last visit at the discretion of the study doctor.

6. If you participate in the study, you must comply with the following:

1) You must participate in the study according to the scheduled procedures of the protocol.
2) During the clinical study, you must not take other drugs (including health functional foods and oriental medicine) without consulting with the study doctor. If you took other drugs, you must inform the appropriate person about the product name, dosing method, and dosing period of the drug.
3) Your study doctor will closely monitor your conditions during the study. Therefore, you must inform your study doctor of all side effects that you experience during the study. Even if it is not during your visit, please inform the study doctor or the provided contact person.
4) If you are a woman of child-bearing potential, you must use proper contraception methods during the study. Accepted contraception methods for this study are as follows.
   - Hormonal contraceptive
   - Intrauterine device or transfer of intrauterine system
   - Barrier method (condom with spermatozoicide, contraceptive diaphragm with spermatozoicide, vaginal sponge, or cervical cap)
   - Sterilization operation (vasectomy of spouse, bilateral tubal ligation)
5) If you realize that you are pregnant during your participation in the study, please notify the study doctor or the provided emergency contact. Even when you end the study, all information pertaining to your pregnancy process and results can be checked and collected.
6) If you are receiving treatment from other medical departments, you must inform the applicable doctor regarding your participation in this study.

7. What are the risks and discomfort expected in this study?

Expected side effects related to the study drug are as follows:

1) Diarrhea, abdominal distention, vomiting, nausea
2) Acne, hives, atopic dermatitis, ulcers in mouth
3) Acute hepatitis, elevated liver index
4) Acute tonsillitis, allergic rhinitis, sore throat, cough, running nose
5) Headache, back pain, chest pain, myalgia, myofascial pain syndrome
6) Diabetes, elevated blood sugar, elevated blood neutral fat
7) Elevated blood creatine phosphokinase, hematuria
8) Decreased leucocyte, decreased platelet, anemia
9) Hypernatremia
10) Elevated blood pressure, fever
11) Urinary tract infection

Since the reporting of such side effects are recording symptoms that occurred during the study, it cannot be definite whether these side effects occurred due to taking the drug. The study drug of this study is commercially available as a health functional food and can be purchased in the market. No serious side effects have been reported since its approval as a health functional food. Also, researchers have determined that there were no serious side effects occurred during the studies conducted prior to the official clinical study. However, an unexpected and new side effect that was not found previously may occur in this study. Although most symptoms reported so far have been mild and resolved without particular treatment, a case of hepatitis that can be considered relatively severe has occurred.

In the case of this patient, symptoms of hepatitis occurred even though the drug concentration in the body was low when compared with other patients and therefore, it is still unclear whether the symptoms are related to the drug. Despite this, since there still is a chance that side effects such as hepatitis may occur in this study, your study doctor will check the liver function values periodically and if there are any abnormal findings, appropriate treatment will be provided through additional tests and consultations with a hepatologist. The side effects found in each clinical study conducted in the United States and Korea are as follows. If you experience similar symptoms or have other discomforts, please contact your study doctor immediately to check if a side effect has occurred.

	Dose	Side Effects
U.S. Take once	500 mg	None
	1000 mg	Headache, vomiting
	2000 mg	None
	4000 mg	Nausea, vomiting, urinary tract infection, elevated blood pressure
Korea	500 mg	Elevated liver index, elevated neutral fat level
	1000 mg	Hives

Take once	2000 mg	Acute hepatitis, elevated blood sugar
	4000 mg	None
Korea Take for 14 days	500 mg	Ulcers in mouth, decreased leucocyte count, atopic dermatitis, itchiness, headache, musculoskeletal chest pain
	1000 mg	Diarrhea, nausea, tonsillitis, elevated neutral fat, cough, runny nose, anemia, chest pain
	2000 mg	Nausea, abdominal distention, tonsillitis, leukocytopenia, acne, myofascial pain syndrome
	4000 mg	Tonsillitis, decreased leucocyte count, decreased platelet, diabetes
Korea Take with meal	500 mg	Elevated blood creatine phosphokinase, elevated neutral fat, hematuria, anemia, hypernatremia
	1000 mg	Back pain
	2000 mg	Fever, allergic rhinitis

Furthermore, pain or discomfort related to blood draws and urine collection needed for scheduled tests may be experienced, which are part of the risks or discomforts related to the study. Blood needed for the test will be about 20 mL at most (1.5 tablespoon or 4 teaspoons). Only blood draws will be taken to check the blood count until Day 2~7 and Day 9~14; after taking the drug and during this time, the amount of blood to be drawn will be less than 3 mL. Also, you may need to fast for 8 hours or more before your visit to the hospital.

Although the amount of blood draws planned for this study is about 70 mL, more blood draws may be needed if the study doctor determines that additional tests are required.
Generally, there is a low possibility of developing health issues caused by the amount of blood draws scheduled for this study, since blood makes up about 8% of our body weight. However, the study doctor will closely monitor the process since there is a possibility that blood toxicity may occur from the drug for your anti-cancer treatment and the study drug you will be taking for this study.

Biopsies, including blood or urine collected from you, will be disposed according to appropriate procedures after the assessment.

8. What are the benefits of taking part in the study?

Taking part in this study may or may not give you direct medical benefits. However, clinical study may help to develop a new therapy for patients who have similar symptoms or diseases that you have.
You will take part in this study since side effects caused by anti-cancer drugs including neutropenia may occur due to the use of anti-cancer drug, not EC-18. Therefore, you may receive bone marrow growth factors, such as Granulocyte Colony-Stimulating Factor (G-CSF) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), based upon the judgment of the investigator in charge after receiving the first anti-cancer drug treatment and EC-18

during the same anti-cancer drug treatment in this study. Granulocyte Colony-Stimulating Factor (G-CSF) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) are treatment agents that prevent or lower the severity of neutropenia.

9. What is the cost for participating in this study?

You will be provided with treatments (including weekly anti-cancer treatment) or tests needed to conduct the clinical study or the study drug. Therefore, you will not be responsible for any costs related to your participation in this study. Aside from this, you will be provided with a transportation allowance of 100,000 KRW for every regular visit. However, there will be no other monetary benefits or compensation for your participation in the study.

10. What other choices do I have?

Currently, a treatment method that administers bone marrow growth factors, such as G-CSF (Granulocyte Colony-Stimulating Factor) and GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor), is being used as the primary method to prevent neutropenia induced by chemotherapy or decrease the severity. However, when using this type of therapy, side effects or allergic responses frequently occur. Therefore, an adjuvant therapy that can be easily administered with reduced burden for cancer patients who are already exposed to various side effects from previous chemotherapies needs to be developed.

11. Compensation and treatment plan in the case of injury are the following:

If you have been injured due to your participation in this study, your study doctor will exercise the best efforts to treat your injury and the sponsor (Enzychem Lifesciences Corporation) will cover the treatment cost in accordance with the Policy on Compensation for Injured Subjects.

12. What are the rights of subjects who take part in this study? Can I refuse to take part in this study or request to withdraw during the study?

If you take part in the study, your legal rights and liabilities will remain.
Taking part in the study is a voluntary decision and you may freely refuse to participate in the study. Even if you already participated in the study, you are free to withdraw from the study at any time if you wish. If you refuse to take part in the study or withdraw your participation in the study, you will not be subject to any disadvantages in receiving other medical procedures and treatments.

Your study doctor will inform you or your guardian in the event that any new information is collected that may affect your willingness to continue in the study as soon as possible. You may refer to such information in order to decide whether to continue in the study.

13. Is it possible to terminate my participation during the course of the clinical study?

Based upon the situation observed during the clinical study, if it is decided that continuing the study is not advised, the principal investigator or sponsor may terminate the study. Also, the study may be terminated according to the determination of the Institutional Review Board (or Ministry of Food and Drug Safety).

In addition, the following are other reasons for terminating the study:

1) When the subject or subject's representative requests to withdraw his/her participation in

the study
2) When continuation of the study is difficult due to occurrence of side effects
3) When the protocol is not followed
4) When the subject received medications or procedures prohibited in this study or such treatment options are determined as required
5) When follow-up procedures are not available due to missing visit(s) of the subject
6) When the subject has become pregnant
7) When continuing participation of the subject is not advised under the discretion of the investigators

14. Your confidentiality of personal information will be managed by the following methods:

Your information collected from this study will be protected by applicable laws and regulations including the Privacy Protection Act. Thus, your study doctor will explain information such as items, purpose, retention period, use, and provision of personal information to be collected during this study (including sensitive information) to obtain your consent. In addition, information collected from you will be treated as anonymous and records that can identify you will be kept confidential. On the other hand, your information can be used domestically and internationally upon request from the sponsor for the purpose of publication. Even though study results may be published, your identity will be kept confidential.

The purpose of collecting/using your personal information and sensitive information is to utilize such information for the study and to perform organizational, analysis, and report-related tasks regarding the study results.

In order to do so, your personal information and sensitive information will be collected as shown below:

Information Type	Detailed Items
Personal Information	Name (including initials), age (year and month of birth), gender, address, contact number, bank account number, etc.
Sensitive Information	Medical records (medical history, test results, concomitant medication, etc.).

Your personal information and sensitive information shown above may be retained and utilized within the scope of the purpose of this study for up to 5 years from the completion of the study.

Information collected during this study that includes your personal information, your medical records monitored by the study doctor, health-related information, and sensitive information may be provided to Enzychem Lifesciences Corporation, C&R Research Co., Ltd. (assigned to a specific part of the study), and Biocore Co., Ltd. (a central laboratory related to the study), for the purpose of organization, analysis, and reporting of the study data. Study data to be provided as shown above will be provided in the form of study identification codes from which the information that can directly identify you, such as your name or address, is removed. In addition, study data can be provided to the MFDS, U.S. Food and Drug Administration (FDA), and/or institutional review board (IRB) individually or along with other study data within the purposes specified in applicable laws and regulations.

The sponsor (Enzychem Lifesciences Corporation), MFDS, and U.S. FDA may directly view your data for the purpose of validating the study procedures and the reliability of the study data. If you sign this informed consent form, it means that you agree to allow monitors, auditors, IRB members, and Minister of MFDS to directly view your medical records within the purposes specified in the applicable laws and regulations without infringing your confidentiality. Of course, this data will only be used by the parties specified above for the purposes of carrying out their obligations pertaining to the study.

You may refuse to allow your personal information and sensitive information to be collected and used, and to provide your information to third parties including Enzychem Lifesciences Corporation, C&R Research Co., Ltd., MFDS, and/or IRB. If you do not agree to collection and use of your personal information and supply of your information to third parties, you will not be able to take part in this study. However, other than that, you will not be subject to any other disadvantages.

15. Emergency Contact

If you need more information or need to contact anyone for medical purposes pertaining to this study, you may ask anything at any time. The contact information of the study doctor and study staff is as follows:

Study doctor:
Contact:
24 hour phone number:

Study staff:

Contact:

If you have any questions pertaining to the rights of the subject, please contact us with the following contact information:

▣▣ Institutional Review Board of the Hospital

Contact:

If you have read the above information sheet and agree to take part in this study, please sign and date the informed consent form. The informed consent form is a form which has obtained written approval by the institutional review board.

Informed Consent Form

Study Title: Dose-Escalation, Open-label, Multicentre Clinical Trial to Assess the Safety, Tolerability and Pharmacokinetics of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen

1. I have been provided with detailed explanations for all information about the study and collection and use of my personal information (including sensitive information) from the study doctor and I fully understood such information.
2. I understand that I am free to decide whether to take part in this study and whether to allow my personal information (including sensitive information) to be collected and used. Also, I understand that I am free to withdraw my consent at any time during the study period and I will not be subject to any penalties as a result of my withdrawal.
3. I understand that I can ask any questions related to the clinical study at any time.
4. I understand that my medical records can be directly viewed within the purposes for this study and that my information can be collected, processed, and used. Also, I understand that my information may be transferred to third parties upon valid requests from them.
5. I understand that I will have one copy of the subject information sheet and the informed consent form respectively.

□ I fully understand and agree to the explanations about my personal information being collected, used, and provided to third parties.
□ I fully understand and agree to the explanations about my sensitive information being collected, used, and provided to third parties.
□ I voluntarily agree to be part of this study.

Subject	Name: _____	(Signature)	Year Month Day
Legally Accepted Representative*	Name: _____ Relationship to Subject: _____	(Signature)	Year Month Day
Impartial Witness**	Name: _____	(Signature)	Year Month Day
Investigator***	Name: _____	(Signature)	Year Month Day

*These persons can be parental guardian, spouse, or guardian of the subject, if the subject cannot decide whether to take part in the study.
**These persons will attend the written consent process to read the written informed consent form and all written information provided to the subject, if the subject or representative cannot read the informed consent form, subject information sheet, and/or any written information.
***Principal investigator or doctor, dentist, or Korean medicine doctor appointed by the principal investigator.

Attachment 2: Victim Compensation Policy

Clinical Trial Compensation Guidelines

1. Basic principles

1) Enzychem Lifesciences Corporation (hereinafter referred to as "Company") is liable for any bodily injury (including death) to the subject of a clinical trial.

2) Compensation will be paid for injury caused to a subject attributable to participation in the clinical trial, when the use of a trial medicine has been the direct cause of the injury or where the Company fails to prove that the cause of the injury is not related to the trial medicine in question.

3) Compensation will be paid for injuries of an enduring and disabling character, as well as temporary pain or minor injuries that can be easily treated.

4) The Company does not accept liability for injury caused by serious faults in implementing the clinical trial on the part of its research supervisor and person in charge.

5) The Company will take out an insurance policy to cover any injury that may occur in this clinical trial.

2. No compensation will be paid in the following cases:

1) Any injury occurring during a clinical trial that is not sponsored by the Company or any injury caused by an adverse reaction to the medicinal product under trial that is not provided by the Company;

2) Any failure of a medicinal product to have its intended effect or to provide any other benefit:

3) Any harm caused by departure from the agreed protocol; or

4) Any harm arising from negligence by clinical trial subjects or their guardians.

3. Criteria for assessment of compensation

1) The amount of compensation paid should be appropriate to the nature, severity and persistence of the injury and should in general terms be consistent with the damages commonly awarded for similar injuries by the Korean Courts.

2) If there exists a difference of opinion between the subject and the Company as to the appropriate level of compensation, it is recommended that both parties seek the opinion of a mutually acceptable expert to reach an agreement and the payment is made accordingly.

With reference to the aforementioned provisions, the Company pledges to make sure that subjects participating in this clinical trial will not be harmed, and will take full responsibility should any problem occur, in accordance with these guidelines.

Date _____

Signature _____

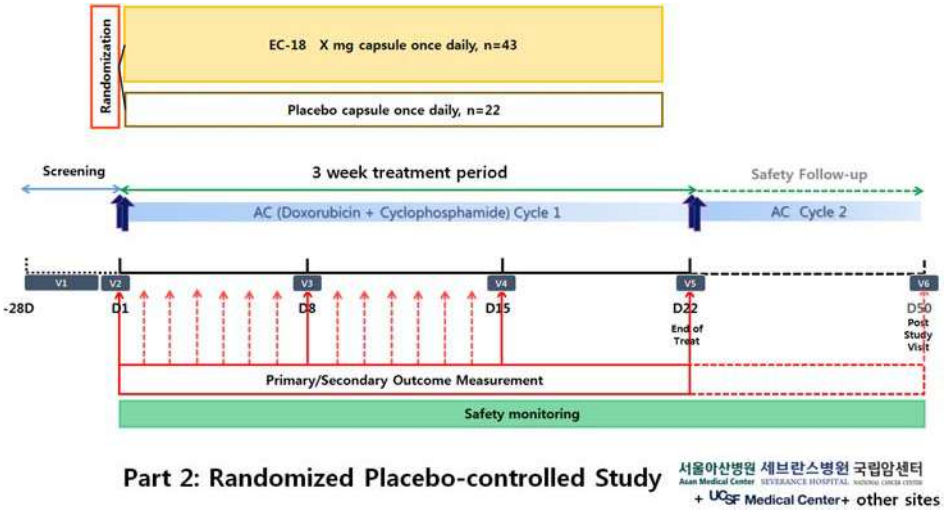
Enzychem Lifesciences Corporation, Ki-Young Sohn, CEO

Attachment 3: Placebo-controlled Part 2 - Protocol

Attachment 3. Synopsis of Additional Plan for Part 2 of Placebo Control Clinical Study

The part 2 of this study will be designed as a randomized, placebo control, double blind, and dose expansion arm. This study may be conducted by revising the protocol based on the analysis results after the clinical study is completed. Since all the subjects must be administered with a fixed dose of EC-18 which has been confirmed to be safe and have the most superior effect on the absolute neutrophil count or a placebo in part 1 of the study, the Data and Safety Monitoring Committee will establish a baseline neutrophil count, review other areas such as safety and pharmacodynamic activity to support the selection of doses in the part 2 of the placebo controlled study. Additional clinical study may be conducted only if the analysis data are submitted to Ministry of Food and Drug Safety (hereinafter referred to as MFDS) and the Institutional Review Board and the protocol of Part 2 is approved. In this case, Part 2 of the clinical study in which 65 subjects with progressive breast cancer are enrolled based on the calculation basis of subjects is reflected in the protocol as an addition and the subjects will be randomized to the EC-18 arm and control arm at the ratio of 2:1.

After completing this clinical study, the Data and Safety Monitoring Committee will review the clinical study's safety and pharmacodynamic activity and submit the summary data to MFDS and Institutional Review Board for discussion to determine dose, usage, and dosing period. Thus, this synopsis describes the rationale for designing the part 2 of this study and preliminary plans for sub-studies that will be added to the main study.



[Synopsis of the Additional Placebo-controlled Study Plan]

USAGE AND DOSE OF THE INVESTIGATIONAL PRODUCT

Similar to the clinical study, placebo-controlled clinical study will also consist of up to 4 weeks of screening period, 3 weeks of treatment period, and 4 weeks of safety follow-up period.

During the treatment period, a total of 65 subjects will take daily dose of EC-18 that has been found through the study or the placebo (EC-18: placebo = 2:1). CBC and differential blood count will be monitored for 15 days during the first cycle of chemotherapy or until the ANC improves to ≥1.0 x10^9/L. Safety analysis and monitoring of adverse events and combination drugs will be carried out during the entire period of the clinical study.

OVERVIEW OF STUDY DESIGN

The placebo-control study was designed as a randomized, placebo-controlled, and double-blind study. All subjects will receive EC-18 at the dose which has been found to be safe and most effective for the absolute neutrophil count (according to the established baseline value of DSMC) or placebo. Data and Safety Monitoring Committee will review the study's safety and pharmacodynamic activity to aid in selecting the dose in the placebo-control study. The goal is to enroll 65 subjects with advanced breast cancer who will be randomized to EC-18 arm and control arm at the ratio of 2:1.

In the placebo-control study (part 2), after taking the given doses for each arm, the Data and Safety Monitoring Committee will review the study's safety and pharmacodynamic activity and submit summary data to MFDS and IRB. Subsequently, usage, dose, treatment period, and patient arm will be decided to conduct the study with the amended protocol.

SUBJECTS' PARTICIPATION PERIOD

1) **Placebo-control group:**
   - 7 weeks (3 weeks of treatment period and 4 weeks of safety follow-up);
   - Efficacy of EC-18 will be monitored for 3 weeks (Cycle 1) and safety will be monitored for
     7 weeks by adding 4 weeks of follow-up period to the Cycle 1 (3 weeks).

NUMBER OF SUBJECTS

The objective of the randomized study is to have a total of 57 subjects who complete the study at the ratio of 2:1 (38 subjects for the EC-18 treatment arm and 19 subjects for the control arm). The total number of subjects is 65 including the withdrawal rate of 10%.

The rationale of the number of subjects is the following:

- This study's primary endpoint is the duration of Grade 4 neutropenia.
- According to the reference, the mean duration of Grade 4 neutropenia was reported as 3.8 days during Cycle 1 of the double chemotherapy that showed mild risk level for febrile neutropenia (A del Giglio et al, 2008).
- The objective is to confirm 33% improvement (reduction) of duration of Grade 4 neutropenia which is a primary endpoint after taking the investigational product (target duration of Grade 4 neutropenia: 2.5 days).

- After establishing the ratio between the investigational product arm and the control arm to 2:1, the number of subjects that has Type I error 0.05 and 80% of power was calculated as 38 subjects for the control arm and 19 subjects for the placebo arm with PASS software (version 11).
- Thus, in consideration of withdrawal rate of 10%, the Part 2 randomized study of this protocol was designed to have a total of 65 subjects (43 subjects for the investigational product arm and 22 subjects for the control arm).

METHOD OF RANDOMIZATION AND ADMINISTRATION

Subjects will receive the dose determined by the Safety Monitoring Committee in accordance with the efficacy assessment on safety, ANC, and other factors for subjects randomized to each of dose groups and the planned ratio of randomization between EC-18 and placebo is set to 2:1.

RANDOMIZATION AND BLINDING PROCEDURES

Subjects will be randomized to EC-18 or to placebo at the ratio of 2:1. Since this study is a double blind study, the subject, the investigator, study team involved with the subject's clinical treatment, and the sponsor or its designee involved with the study will not know which treatment arm a particular subject is randomized. It may be unblinded only in emergency situations when it is required to protect the subject's life or physical well-being.

The emergency unblinding procedure will be provided by a CRO staff and will be indicated in the study center's reference manual.

A subsequent written report including all relevant details should be submitted to the study's medical monitoring personnel within 24 hours after unblinding.

In the event that the investigator, study team at the site where the evaluation is conducted or the subject is unblinded, the applicable subject must stop his/her participation for this study and undergo procedures related to withdrawal.