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, Tolerability and Pharmacokinetics of EC-18 in Women with Advanced Breast Cancer Receiving AC Regimen

Statistical Analysis Plan

Based on Protocol Version 7.1, 13Aug2019

Version 2.0
12Feb2020

Prepared by:



Statistical Analysis Plan REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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Modification Log

Date	Made by	Notes
12Feb2020	Emilea Norris	Version 1.0 of the SAP was based on Protocol Version 5.1. Version 2.0 of SAP based on updates for in-between versions as follows. Updates from Protocol Version V5.1, V5.2, V6.0, V7.0, and V7.1 include ● Synopsis ● Changes in objectives and endpoints ● Sample size and study design ● Up to date schedule of assessments table/footnotes added. Sponsor provided. Analysis conventions were updated to reflect ● 95% confidence intervals will only be presented if appropriate ● Number of missing values will be presented only if appropriate Primary endpoint analysis ● Wilcoxon rank sum was mentioned in first version of SAP and has been removed due to the low number of subjects and high number of cohorts. ● Clarified descriptive statistics for the duration will be provided. ● Removed “time to reach assignment of not neutropenia grade 4” as this was not part of the protocol and recovery is part of secondary endpoint section. ● Clarified neutropenia/ thrombocytopenia events and grades are recorded in the clinical database (AE eCRF page). Other areas include ● Replaced “treatment group” with “cohort”. ● Denoted concentration and PK summaries will be handled by Enzychem and separately from this plan. ● Added baseline definition. ● Added disposition, protocol deviations, ● Added BMI calculation ● Added summary of exposure and compliance ● Physical exam and ECOG will only be listed. ● Vitals summary will include weight and ECG.

		Vitals, weight ECG, and Chest x-ray will be listed, not provided in summary tables. Added LEVF. ● added definition for TEAE ● added definition for neutropenia, febrile neutropenia ● added definition for prior and concomitant medication ● added definition for Oral or IV antibiotics ● added definition for G-CSF medications ● laboratory data will only be provided in a listing, no summary tables. ● added partial date imputation rules ● clarified sections where summary tables were included in previous SAP version, and now will only be provided as data listing. o For example, vitals and laboratory data will not be tabular, but will only be provided in a listing. Screen failures occurred and noted their data will show in listings as available.
28Jun2018	Rhonda Roberts	Version 1.0 of SAP based on Protocol V5.1

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1. Synopsis

In the studies on the Mechanism 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 including febrile 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-control study with 48 patients with metastatic pancreatic cancer, the 16 patients who received EC-18 experienced lower syndrome of infection and neutropenia as compared with control group (32 patients received placebo).

This clinical trial is a Phase 1b/2 implementing the "3+3" dose escalation design with once-a-day administration to advanced breast cancer patients in 4 cohorts. The aim is to primarily determine a maximum safe dose (i.e., maximum tolerated dose, MTD) and possibly, observe dose limiting toxicity (DLT).

After reviewing the results from the four first cohorts, this trial was revised to include 2 additional cohorts. The rationale was based on MTD and DLT were not found in the four first cohorts.

This analysis plan is based on Protocol Version 7.1 13Aug2019. The last English translated full protocol is Version 5.1. Protocol versions after V5.1 are summary of change documents. Enzychem reviewed this analysis plan to confirm interpretation of the summary of changes were addressed in this analysis plan. Enzychem also compared the analysis plan to the final protocol version to confirm analyses were addressed.

2. Study Objectives

2.1. Primary Objective

The primary objective is to demonstrate duration of grade 4 neutropenia during cycle 1 of chemotherapy (i.e., the first chemotherapy cycle) when EC-18 is administered to patients with metastatic or recurrent breast cancer whose risk level for febrile neutropenia is low and who are receiving second line or higher chemotherapy that incorporates doxorubicin/cyclophosphamide (i.e., AC regimen). Please refer to the primary efficacy endpoints (SAP Section 5.1).

2.2. Secondary Objective

The secondary objective is to determine the MTD from subjects experiencing DLT and evaluate Pharmacokinetics (PK) parameters. Please refer to the secondary, PK, and safety endpoints (SAP Section 5).

3. Sample Size and Study Design

3.1. Sample Size

This is the original sample size idea for the study which was employed for the enrollment of the first 4 cohorts. 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 subjects each were recruited. This trial includes medium risk due to ≥50%, high rate of screening failures/ drop-outs and so, for enrollment management, actual subjects should have been enrolled considering extra subject(s) per cohort. A total of 12 subjects were 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 are enrolled and administered the same dose. If the second DLT occurs in the expanded cohort, no more subjects are added and dose escalation is stopped. If no DLTs are observed, the dose is escalated to the next dose level. At the four first cohorts, the dose level at which a DLT is observed in more than 2 of 6 subjects are defined as exceeding MTD, and 3 additional subjects are administered the previous dose level. The MTD is defined as the highest dose at which no more than 1 of 6 subjects experienced a DLT. Subjects with a DLT must be discontinued from the study.

This is the revised sample size approach for the study. After reviewing the results from the four first cohorts, this trial was revised to include 2 additional cohorts. The rationale was based on MTD and DLT were not found in the four first cohorts. This trial implements a cohort expansion with both cohorts 5 and 6 enrolling at the same time.

Instead of 4 cohorts with 6 subjects each, there are now 6 cohorts and with 6 subjects each. Enzychem employed a model-based design by mCRM (modified continual reassessment method) using Bayesian model-based method.

3.2. Study Design

This study is an open-label, dose-escalation trial to evaluate the safety, tolerability and pharmacokinetics of EC-18. All subjects in each cohort group will be administered the study drug, EC-18 within 30 minutes after 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 6.5 of the protocol.

The four first cohorts were completed as follows:

- The four doses planned were 500 mg, 1000 mg, 1500 mg and 2000 mg. In the event of occurrence of a DLT, three subjects are added to the corresponding dose group. The DSMC reviewed the safety of each dose group to determine dose escalation.

Protocol Version 7.0 introduced the cohort expansion:

- After the completion of the four first cohorts, then a cohort expansion was planned (adding cohorts 5 and 6). Both cohorts enrolled subjects and provided treatment at the same time. Cohort 5 is a 3000 mg dose (6 capsules of EC-18 500mg) and cohort 6 is a 4000 mg dose (8 capsules of EC-18 500mg). Each cohort will enroll at least 6 subjects.
- Once a DLT is observed in one of 3 subjects per cohort, 3 additional subjects are enrolled and receive the same dose. Once the 2nd DLT is observed, enrollment is stopped, and the study is completed.
- The DSMC will review the safety of each dose group prior to advancement to the next trial (which is the planned Phase 2 trial).

The cohorts and dose levels are as follows:

Cohort	**EC-18 Dose/Day**	**Total Number of Capsules Expected to be Taken**
1	500 mg (1 capsule)	21
2	1000 mg (2 capsules)	42
3	1500 mg (3 capsules)	63
4	2000 mg (4 capsules)	84
5	3000 mg (6 capsules)	126
6	4000 mg (8 capsules)	168

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

4. Schedule of Assessments

The schedule of assessments presented were translated to English by Enzychem from the protocol.

Assessment	Screening	Treatment Phase			Follow-up	
	Week -4 to -1	Week 1	Week 2	Week 3	Week 4	Week 6
	Day -28 to -1	Day 1	Day 8	Day 15	Day 22[o]	Day 36[p]
	Visit 1[q]	Visit 2	Visit 3 (±2 days)	Visit 4 (±2 days)	Visit 5 (±2 days)	Visit 6 (±2 days)
Informed consent	**X**	NA[a]	NA	NA	NA	NA
Group assignment	NA	**X**[b]	NA	NA	NA	NA
Inclusion/exclusion criteria	**X**	**X**	NA	NA	NA	NA
Medical history	**X**	NA	NA	NA	NA	NA
ECG[c]	**X**	**X**[d]	NA	NA	(**X**)	(**X**)
LVEF	**X**	NA	NA	NA	NA	NA
Chest X-ray	**X**[d]	NA	NA	NA	(**X**)	(**X**)
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**
Weight and height[e]	**X**[e]	**X**	**X**	**X**	(**X**)	(**X**)
Vital signs	**X**	**X**	**X**	**X**	(**X**)	(**X**)
Physical examination	**X**[f]	**X**[g]	**X**[g]	**X**[g]	(**X**)	(**X**)
ECOG performance status	**X**	**X**	NA	**X**	(**X**)	(**X**)
CBC with differential[h]	**X**	**Daily (omitting Day 3 and 4)**[d, h]			(**X**)	(**X**)
Serum chemistry	**X**	**X**[d]	**X**	**X**	(**X**)	(**X**)
Coagulation tests	**X**	**X**[d]	**X**	**X**	(**X**)	(**X**)
Urinalysis	**X**[d]	NA	NA	NA	NA	(**X**)
Urine pregnancy test	**X**	**X**[d]	NA	NA	NA	NA
Virus serology	**X**	NA	NA	NA	NA	NA

Reticulocyte count	NA	**X**	**X**	NA	NA	NA
EC-18[i]	NA	**Given orally once daily from Day 1 through Day 21**[i]			NA	NA
Chemotherapy[j]	NA	**X**[k]	NA	NA	**X**	NA
Adverse events[l]	**X**	**X**	**X**	**X**	**X**	**X**
Admission[m]	NA	**X**	NA	**X**	NA	NA
PK sampling[n]	NA	**X**	NA	**X**	NA	NA

CBC = whole blood count and differential blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group
[a]NA = Not applicable
[b]All subjects should take the study drug and receive chemotherapy on Day 1 at Visit 2.
[c]ECG must be measured before blood sampling at any visit.
[d]CBC, serum chemistry, Coagulation tests, Urine pregnancy test, Urinalysis, Chest X-ray and ECG may not need to repeat on Day 1 if any test was performed within 1 week prior to Day 1/Visit 2.
[e]Height is measured at Screening visit only.
[f]includes that: overall appearance, head, eyes, nose, throat, neck, cardiovascular system, lung, abdomen, chest, lymph node, limb, nerve system, skin and musculoskeletal system
[g]includes that: overall appearance, cardiovascular system, lung, abdomen, chest, lymph node and some systems, and may include that: any part(s) or system(s) to evaluate any adverse event(s)
[h]includes that: red blood cell count, hemoglobin, hematocrit, red blood count, red blood cell index, white blood cell count, differential blood counts (absolute or percentage) and platelet count. The CBC testing with differential blood counts must be conducted at Day 1, 2, 5 and more until ANC value is recovered by 1.0 x 10^9/L more (except for Day 3 and 4/ optional on Day 22 and 36).
[i]The study drug is administered on both, Days 1 and 2, and on both Days 15 and 16 in hospitalization for Visit 2 and Visit 4, respectively. Besides them, the study drug is self-administration at home recording both, date and time taken, vomiting with time if occurred, any reason if missed administration in the patient diary.
[j]Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Prior to chemotherapy, any risk of heart failure must be assessed by a total cumulative dose of anthracycline and LVEF measurement. Chemotherapy can be delayed until any abnormal finding in clinical laboratory results will be recovered and must not exceed 3 weeks (i.e., 21 days).
[k]The Cycle 1 of chemotherapy is started on Day 1 (Visit 2) after enrollment and adverse events should be assessed during and after chemotherapy.
[l]Adverse event must be assessed with data collection every visit. To follow up adverse event(s) occurred, the subject must conduct both, Visit 5 and 6. In case of an adverse event is suspected to relate to the study drug, EC-18, investigator might ask Data and Safety Monitoring Board (DSMB) to continuously follow-up the adverse event.
[m]The subject conducts all procedures on both, Days 1 and 2, and on both Days 15 and 16 in hospitalization for Visit 2 and Visit 4, respectively.
[n]Blood sampling for PK evaluation is conducted at 0 (before administration of the study drug), 1, 2, 4, 6, 8, 10, 12 and 24 hr after administration in hospitalization for Visit 2 and Visit 4, respectively.
[o]At Visit 5, concomitant medication(s) and adverse event(s) should be examined by investigator and clinical laboratory tests might be conducted under investigator's discretion accordingly. And, the Cycle 2 of chemotherapy will be started under a subject's condition.
[p]At Visit 6, concomitant medication(s) and adverse event(s) should be examined by investigator and clinical laboratory tests might be conducted under investigator's discretion accordingly. And, any dropped-out subject must conduct all procedures of Visit 6 as End of Study (EOS) visit.
[q]Visit 1 date is the same date of obtaining Informed Consent Form (ICF) from a subject.
※Any subject(s) who discontinued a study drug should return their drugs with the bottle, included in the safety population and should be examined by a physician for her experience of any AE(s) on Day 22 (Visit 5) and 36 (Visit 6), respectively. To follow up adverse event(s) occurred, the subject must conduct both, Visit 5 and 6. In case of an adverse event is suspected to relate to the study drug, EC-18, DSMB might ask investigator to continuously follow-up the adverse event.

5. Study Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the duration of grade 4 neutropenia during cycle 1 of chemotherapy.

5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

1. Frequency of Grade 3-4 neutropenia (according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 4.03 version)
2. Frequency of febrile neutropenia (according to NCI CTCAE 4.03 version)
3. Time for depth to ANC nadir (defined as the patient's lowest ANC in Cycle 1) and, to ANC recovery to Grade 2 or lower neutropenia in Cycle 1
4. Frequency of oral or Intravenous (IV) antibiotic use
5. Frequency of granulocyte colony stimulating factor (G-CSF) treatment

5.3. Pharmacokinetic [PK] Endpoints

The following PK parameters are analyzed separately by Enzychem:

- $C_{max,}$ $AUC_{0\text{-}t}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, T_{max}, λ_z, $t_{1/2}$, $C_{max,ss}$, $C_{min,ss}$, $AUC_{0\text{-}\tau}$ (CL, Vss)

5.4. Safety Endpoints

The safety endpoints include the following:

1. All AEs, Treatment Emergent Adverse Events (TEAEs), SAEs, and frequency of AEs/TEAEs/SAEs caused any study drug discontinuation
2. Clinical laboratory test results (analysis of each result in hematological test, blood chemistry test, coagulation test and urine test) - To analysis change from baseline; looking at absolute differences (changes) from baseline
3. The measurement results for vital signs, weight and 12-lead ECG - To analysis change from baseline; looking at absolute values and differences (changes) from the baseline

6. General Analysis Conventions

All tables, figures and listings will be produced using SAS (V9.4 or a more recent version). Unless otherwise stated, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, standard deviation (SD), median, minimum, maximum, and number of subjects (N). A 95% confidence interval for the mean and number of missing subjects or data points may be provided if appropriate. Minima and maxima will be quoted to the number of decimal places as recorded in the electronic Case Report Form (eCRF); means, SDs and medians will be quoted to one further decimal place. Percentages will be rounded to one decimal place.

Subjects who dropped out from the analysis will have their data analyzed to the point of drop-out.

Baseline will be the last non-missing assessment on or prior to the first dose date (and time if available).

Tables will be displayed by cohort unless otherwise stated. Screen failures will be included in selected table summaries. Listings will display for “All Subjects” so that screen failures will be included.

The PK statistical analyses are conducted and provided separately by the Sponsor. These analyses may be included in the Clinical Study Report (CSR) as an appendix.

7. Definition of Statistical Significance

This study assesses the safety and tolerability of the study drug as assessed by physical examination, vital signs, weight, clinical laboratory tests, ECG and AE evaluations. If necessary, any additional test(s) might be performed under discretion by sponsor, investigator or medical monitor. 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. Albeit there are no specific hypotheses in this study, 95% confidence intervals and associated p-values may be reported to summarize magnitude of associations or differences if appropriate.

8. Analytic Populations

8.1. Full Analysis Set [FAS] Population

The FAS population is defined as all subjects administered at least one dose of a study drug having at least one primary efficacy assessment after enrolled at baseline visit (i.e., Day 1/ Visit 2). All efficacy assessments will be analyzed by the FAS population.

8.2. Safety Set Population

The safety population is defined as all subjects administered at least one dose of a study drug. Any subject who failed to provide data necessary to interpret endpoints will be included in the safety population.

9. Analysis and Summaries

9.1. Descriptive Statistics

For continuous and pseudo-continuous variables, the number of observations, mean, standard deviation, median, minimum, and maximum will be given. For yes/no, categorical, and/or ordinal variables a simple count and percent or frequency will be given. Other statistics may be considered if necessary.

9.2. Disposition, Demographic, Baseline Characteristics, and Deviations

A summary of disposition will include subject counts for screened, screened failure, enrolled, completion status, reasons for early termination, and analysis populations by cohort. Disposition and inclusion/exclusion status will also be provided in a listing.

Demographic and baseline characteristic data will include age (based on date of informed consent), height, and weight, and body mass index (BMI). Please note, gender is not summarized due to all subjects being female. Similarly, race and ethnicity are not summarized due to all subjects being Korean. Demographic and baseline characteristic data will be summarized by cohort and also provided in a listing.

BMI (kg/m^2) will be calculated as weight (kg) divided by [height (cm) divided by 100]^2.

Protocol deviations will be collected during the study period. A classification (like major and minor) will be assigned by the Clinical Operations team and confirmed by medical monitor and Enzychem team review prior to final database lock. The classification will be summarized by cohort and provided in a listing as appropriate.

9.3. Medical History

Medical history and breast cancer history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The prior cancer treatments (surgery, radiotherapy, and chemotherapy) will be coded using the WHO Drug dictionary (WHODD). Each of these will be provided in a listing.

9.4. Virus Serology

Virus serology is collected at screening will be provided in a listing.

9.5. Efficacy Analyses

9.5.1. Definition of Primary Endpoint

To evaluate the primary endpoint and safety, Complete Blood Counts (CBCs) with differential is performed daily at pre-treatment (at screening) and on Days 1, 2, 5 and continuing until ANC value is recovered to ≥1.0 x 109/L more, except for both Days 3 and 4 and on each Day 22 and 36 under discretion by investigator (See Protocol Sections 14.2.1 and 14.4.8). The grade for neutropenia is assessed according to Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.03 version. Febrile neutropenia is assessed by both, ANC value and body temperature according to NCI CTCAE version 4.03. Refer to the NCI CTCAE definition for neutropenia and febrile neutropenia.

All episodes of neutropenia and febrile neutropenia (FN) are collected as AE/SAEs which will be assessed by SAE criteria (See Protocol Section 15.1.2) on the AE eCRF page with necessary information such as causality, severity and so on.

For the analysis purpose, the MedDRA coded preferred term of “neutropenia” and “febrile neutropenia” will be used to identify occurrences.

9.5.2. Primary Efficacy Analysis

The mean duration, in days, of assigned grade (G) 4 neutropenia will be summarized for each cohort. Descriptive statistics will also be provided.

- The duration of G4 neutropenia will be calculated as the number of days the adverse event was experienced.
    - The AE must start on or after the first dose date of EC-18.
    - Duration will be calculated as AE end date minus AE start date and, plus 1 day.
    - Subjects who did not experience the event will have a duration of 0 days.

9.5.3. Hypothesis

No formal hypotheses testing is performed in this study.

9.5.4. Secondary Efficacy Analysis Endpoint

1. The number and percentage of subjects who experienced G3 or 4 neutropenia, G3 or 4 febrile neutropenia and/or G3 or 4 grade thrombocytopenia (see NCI CTCAE Version 4.03) are summarized by cohort and 95% confidence interval for ratio is also presented. The 95% confidence interval may not be provided due to a small number of subjects or events.
    - Thrombocytopenia events will be identified by the MedDRA coded preferred term.
2. The incidence rate of febrile neutropenia will also be presented. The incidence rate will be calculated as the number of events divided by the number of subjects in the cohort, then multiplied by 100.
3. The time it takes for neutropenia to recover is defined as the time until G3 or 4 neutropenia recovers to grade 2 or lower. This is based on adverse event coding and grading. Kaplan-Meier estimates and 95% confidence interval for the median value will be summarized. The results may be summarized in a plot. Descriptive statistics may be provided instead of the Kaplan-Meier estimates (and confidence intervals) due to a small number of subjects or events.
    - In addition, descriptive statistics will be provided for the lowest level of ANC during treatment periods for each cohort. ANC results are provided by the central laboratory and will be used for these ANC summaries. ANC results provided from the local laboratory will be presented in a listing.
    - Please note, the subject's ANC was monitored through the study. Subjects who have not reached the target ANC level will be early terminated on the last laboratory assessment date. This case will rely on the trial management/protocol. The data provided in the EDC will be used and will rely on early termination dates (or last visit/assessment dates) provided in the EDC.

4. The number and percentage of subjects receiving (oral or IV) antibiotics and experienced febrile neutropenia will be tabulated. Definitions are explained in the concomitant medication section below.
5. The number and percentage of subjects receiving G-CSF and experienced febrile neutropenia will be tabulated. Definitions are explained in the concomitant medication section below.

9.5.5. Pharmacokinetic Analyses

The concentration and pharmacokinetic analyses will be covered in a separate analysis plan. The analyses will be provided by Enzychem.

9.6. Safety Analyses

Descriptive summaries of the safety assessments including vital signs, clinical laboratory tests, and all AEs will be summarized by cohort. Event and subject level statistics will be reported as appropriate.

9.7. Physical Examination and ECOG

Physical Examination and ECOG will be listed only.

9.8. Vitals Signs, ECG, and Chest X-ray

Vital signs results (including weight and height), ECG results, and Chest X-ray findings will be provided in a listing. The left ventricular ejection fraction (LVEF) result will also be listed.

Please note, the safety endpoint section of the protocol states “Vital Signs, weight, and 12-lead ECG -- absolute values and changes from the baseline” were of interest. The SAP clarifies that only the results will be provided in a listing. This is a clarification of the protocol text (see **Protocol V5.1, Section 12.3, safety endpoint #3**).

9.9. Laboratory Assessments

Laboratory assessments will be provided in a listing. Central and local laboratory results will be collected for the study and will be listed separately. Urine pregnancy results will be listed only if available.

Please note, the safety endpoint section of the protocol states “Laboratory test (hematological test, blood chemistry test, coagulation test and urine test result analysis) - absolute values and changes from the baseline” were of interest. The SAP clarifies that only the results will be provided in a listing. This is a clarification of the protocol text (see **Protocol V5.1, Section 12.3, safety endpoint #2**).

9.10. Concomitant Medications

Medications will be coded using the WHODD. A medication can be classified as both prior and concomitant.

- Medications taken prior to the first dose date of EC-18 (not inclusive) will be considered as prior medications.
- Medications taken on or after the first dose date of EC-18 (not inclusive) will be considered as concomitant medications.

Prior and concomitant medications will only be provided in a listing.

The usage of "oral or IV" antibiotics and G-CSF will be provided in a listing for the secondary endpoints. These will be defined as follows:

- Oral or IV antibiotics will be identified as medications with a route of "Oral or Intravenous" and WHO Drug coding. This may require medical review for identification.
- G-CSF medication will be identified on the concomitant medications CRF page (G-CSF is "Yes").

9.11. Exposure and Compliance

The planned dosing schedule for EC-18 is once daily for 21 days.

- Days of exposure will be calculated as Last minus First dose date of EC-18 plus 1 day. Sometimes a subject may forget to take a dose during the exposure period and these skipped days will not be adjusted in the exposure.
- Compliance will be calculated as the number of capsules taken divided by the number of capsules planned to be taken, then multiplied by 100 to convert to a percentage.
    - For example, every subject in Cohort 1 is expected to take 21 capsules. If a subject in Cohort 1 stops study drug early (for example early terminates) before completing the 21 days regimen, the expected number of doses will remain as 21.
    - The number of capsules expected per day will vary per cohort, see SAP Section 3 for details. Everyone is expected to take EC-18 for 21 days.

The number of subjects who received the combination thermotherapy, AC regimen, at each visit will be provided by cohort.

9.12. Adverse Event Reporting

All adverse events are collected from the date of signed consent to the final safety follow-up visit. Adverse events are coded by using MedDRA and grades are assigned based on NCI CTCAE, Version 4.03. A TEAE is an event that started on or after the first dose date.

The event summary will include total count of events, unique count of subjects, and percentage of subjects. The following summaries of AEs will be provided:

- overall summary of TEAE and Serious TEAE categories which may include all TEAEs, Treatment related TEAE, related to treatment TEAEs, TEAEs leading to withdrawal, and TEAEs leading to death;
- TEAEs summarized by system organ class, by preferred term and toxicity grade.

All AEs will be provided in a listing. In addition, AEs leading to withdrawal, AEs leading to death, and Serious AEs will also be listed.

10. Missing Values

No missing value imputation methods will be applied, e.g. the analyses are based on a valid case basis. Prior medication, concomitant medication, and TEAE definitions are sensitive to dates. The following partial date imputation rules can be applied.

Missing	Start Date/Time	End Date/Time
date: only year is available	set month and day to January 01	set month and day to December 31
date: only month and year are available	set day to 01	set day to end of the month
time: if time is not available,	then set to first of the day	then set to end of the day
If date is completely missing	no imputation will be done	no imputation will be done