Official Title:	**A randomized double-blind, placebo-controlled, multicenter phase 3 study to evaluate the safety, efficacy and pharmacokinetics of trilaciclib in patients with extensive stage small cell lung cancer treated with carboplatin and etoposide or with topotecan**
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Statistical Analysis Plan (SAP)
(Part II)

Protocol:	**A randomized double-blind, placebo-controlled, multicenter phase 3 study to evaluate the safety, efficacy and pharmacokinetics of trilaciclib in patients with extensive stage small cell lung cancer treated with carboplatin and etoposide or with topotecan**
Protocol No.:	**B02B00801-TRILA-301**
Sponsor:	**Jiangsu Simcere Pharmaceutical Co., Ltd.**
SAP Author:	[redacted]
SAP Version:	**V1.0**
SAP Finalized:	**February 16, 2022**

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Abbreviations

Abbreviation	Full Name in Chinese
AE	Adverse Events
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
CDK4/6	Cyclin-dependent kinases 4 and 6
CI	Confidence interval
CR	Complete response
CTCAE	Criteria for Common Adverse Events
CYPs	Cytochromase
DCR	Disease control rate
DSN	Duration of severe neutropenia
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESA	Erythropoietin
ES-SCLC	Extensive stage small cell lung cancer
FAS	Full Analysis Set
FN	Febrile neutropenia
G-CSF	Granulocyte colony-stimulating factor
HSPC	Hematopoietic stem/progenitor cells
HGB	Hemoglobin
IL-11	Recombinant human interleukin -11
IRT	Interactive response system
MedDRA	ICH Medical Dictionary for Regulatory Activities
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Disease progression

Abbreviation	Full Name in Chinese
PFS	Progression-free survival
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PLT	Platelets
PPS	Per-Protocol Analysis Set
PR	Partial response
PT	Preferred Term
RBC	Red blood cell
RES	Response Assessment Analysis Set
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
SAE	Serious Adverse Events
SCLC	Small cell lung cancer
SD	Stable disease
SN	Severe neutropenia
SOC	System Organ Class
SS	Safety Analysis Set
TEAEs	Treatment-emergent adverse event
TPO	Thrombopoietin
WHODrug	World Health Organization Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) provides planned analyses and corresponding statistical methods for Part 2 (randomized, double-blind part) of Protocol B02B00801-TRILA-301 Version V1.3.

2. Study Design

2.1. Protocol Synopsis

Protocol synopsis is provided in Appendix 1, study endpoints are listed in the protocol synopsis, and further information is provided in the trial flow chart in Appendix 2.

2.2. Sample Size Determination

The sample size of the second part of this study needs to meet the need to test the efficacy of DSNs in Cycle 1 and is calculated by stochastic simulation. An integrated analysis of the three overseas pivotal studies of Trilaciclib in SCLC showed an approximately 4-day reduction in Cycle 1 DSN in the Trilaciclib group relative to the placebo group. Taking into account the derivation of DSN in Cycle 1, DSN in Cycle 1 is 0 if the subject did not experience any SN during Cycle 1. When there is a large proportion of zero-values, i.e., a large proportion of subjects who do not have any SNs in Cycle 1, the Cycle 1 DSNs more closely follow a Poisson distribution with a mean of -log (proportion of subjects who do not have any SNs in Cycle 1). In the integrated analysis, the proportion of subjects who developed SN during Cycle 1 is 6.7% in the Trilaciclib group compared to 49.6% in the placebo group. Assuming that the proportion of subjects in this study who occurred SN during Cycle 1 is 10% in the Trilaciclib group and 45% in the placebo group, the means of Poisson distributions is 0.105 and 0.598 for the corresponding Trilaciclib and placebo groups, respectively. The stochastic simulation is repeated 10,000 times, each time obtaining the DSN in Cycle 1 from a Poisson distribution and performing comparison between groups by Mann-Whitney-Wilcoxon test, 70 subjects (35 per group) provided approximately 95% power at the test level of $\alpha = 0.05$ (2-sided). Assuming a dropout rate of 12%, the sample size for Part II is 80 subjects (40 per group).

3. Study Conduct

The second part of this study is a randomized double-blind, placebo-controlled study enrolling approximately 80 patients with ES-SCLC, stratified by 1st line vs 2nd/3rd line ES-SCLC, ECOG PS (0-1 vs 2), and presence vs absence of brain metastases, randomized in a 1:1 ratio to Trilaciclib versus placebo where 1st line ES-SCLC patients receive Trilaciclib/placebo in combination with EC regimen (Trilaciclib-EC group and placebo-EC group), 2nd/3rd line ES-SCLC patients will receive Trilaciclib or placebo in combination with Topotecan (Trilacicli-TPT group and placebo-TPT group), and the efficacy of Trilaciclib (prevention of

myelosuppression) will be evaluated with duration of severe neutropenia (DSN) in Cycle 1 as the primary endpoint.

4. Statistical Analysis Methods

The Part 2 of the study will evaluate the myeloprotective efficacy of Trilaciclib treatment (prevention of chemotherapy-induced myelosuppression) based on data from approximately 80 patients with ES-SCLC, evaluate the safety and tolerability of Trilaciclib in patients with ES-SCLC, and explore the anti-tumor efficacy.

4.1. General Principles

Descriptive statistics (mean, standard deviation, median, range, etc.) will be used to summarize continuous variables, and counts and proportions will be used to summarize categorical variables by treatment group. For time-to-event variables, Kaplan-Meier method will be used to estimate the survival function and estimate the median survival time and its 95% confidence interval, and survival curves will be provided.

Unless otherwise specified, the cycle baseline measurement for Cycle 1 is defined as the last available valid measurement within 7 days before the start of study medication on Cycle 1 Day 1; the baseline measurement for subsequent cycles is defined as the last available valid measurement within 3 days before the start of study medication on Cycle 1 Day 1. Unless otherwise specified, study baseline measurements are defined as the last available valid measurement prior to the first dose of study drug. If the last valid measurement coincides with the start date of the first study drug administration, the measurement will be considered as baseline measurement. Adverse events or concomitant medications that occurred on the day of the first dose of study drug are considered postbaseline.

The start date of each cycle is defined as the first day of the cycle, i.e., the date of the first study drug administration of the cycle; the end date of each cycle is defined as the start date of the next cycle, or the first day of the cycle +36 days if the next cycle is not entered.

4.2. Analysis Set

4.2.1. Myeloprotection efficacy analysis set

Full Analysis Set (FAS): All enrolled patients who received at least one dose of study drug according to the intention-to-treat (ITT) principle. Randomized subjects will be analysized according to the assigned group at randomization. Unless otherwise specified, efficacy analyses for myeloprotection will be based on the FAS.

Per-Protocol Analysis Set (PPS): Patients with major protocol deviations that were judged to have a major impact on the results are excluded from the FAS. PPS is a subset of FAS, and the classification criteria need to be finalized before database lock library. The PPS may be used

for analysis of individual myeloprotective efficacy endpoints.

4.2.2. Antitumor Efficacy Analysis Set

Response Evaluable Analysis Set (RES): all patients who took at least one dose of study drug, had measurable disease at baseline, and completed at least one post-treatment tumor imaging assessment. This analysis set will be used for the analysis of anti-tumor efficacy endpoints related to tumor RECIST1.1 assessment.

4.2.3. Safety Analysis Set

Safety analysis set (SS): all patients who have taken at least one dose of study drug. Safety analyses will be based on the SS by actual treatment received.

4.2.4. Pharmacokinetic Analysis Set

PK Analysis Set (PKS): All patients who received at least one dose of the study drug and had at least one valid concentration data of the tested components after drug administration. Pharmacokinetic analyses will be based on the PKS.

Patients will be excluded from the PK analysis set if they had major protocol deviations, inaccessible or incomplete data, or other circumstances that could affect the pharmacokinetic analysis. The list of patients with any major deviation or event significantly affecting PK results and reasons for exclusion should be reviewed and confirmed before database lock.

4.3. Study Population

4.3.1. Subject disposition

The distribution of patients will be summarized based on all screened patients, including patient screening, enrolled medication, reason for end of treatment, reason for withdrawal from the study and inclusion in each analysis set, and listing will be provided in detail.

4.3.2. Protocol Deviations

The number and percentage of patients with major protocol deviations (including major deviations from inclusion and exclusion criteria) during the trial will be summarized, and the reasons for major protocol deviations will be summarized and listed in detail. Patients with multiple major protocol deviations in different categories will be counted in each corresponding category.

4.3.3. Demographic and Baseline Characteristics

Demographic and baseline disease characteristics include age at the time of informed consent, age group (18-65, > 65-75, > 75), gender, vital signs (weight, height, body surface area) at screening, ECOG score, presence of brain metastasis, baseline lactate dehydrogenase (LDH) level, family history, allergic history, smoking history, tumor history and history of tumor radiotherapy.

Descriptive statistics (mean, standard deviation, median, range, etc) will be used to summarize continuous variables, and frequency and percentage will be used to summarize categorical variables.

4.3.4. Previous Medical History, Prior Medications, and Non-Drug Therapies

Previous medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA Chinese version 24.0) and summarized by System Organ Class (SOC) and Preferred Term (PT). Listing will be provided in detail.

Prior medications or therapies is defined as any non-study medications or therapies administered by the patient from 14 days prior to signing informed consent through the first dose of study drug. Patients' prior medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD (March 2021) Chinese version) and will be summarized by chemical subgroup and generic drug name. Listing will be provided in detail.

4.3.5. Concomitant Medications and Non-Drug Therapies

Concomitant medications will be coded using the latest version of WHO-DD and summarized by chemical subgroup and generic drug name, and the number and percentage of patients using concomitant medications will be counted. Concomitant medications and concomitant non-drug therapies will be presented in detail in listings.

The number of cycles with interleukin (IL-11) and thrombopoietin (TPO) administration and the weekly event rate will be summarized and tabulated in detail by patient, respectively.

4.3.6. Subsequent antineoplastic therapy

Subsequent antineoplastic therapy refers to any subsequent non-study oncology agent administered after the first dose of study drug. Subsequent anticancer therapies will be coded using the most recent version of the World Health Organization Drug Dictionary (WHODrug) and summarized by chemical subgroup and generic drug name. The number and percentage of subjects with subsequent anticancer therapy will be summarized by treatment group. Listing will be provided in detail.

4.4. Efficacy analysis of myeloprotection

The efficacy analysis of Trilaciclib for myeloprotection in ES-SCLC patients will be based primarily on the Full Analysis Set (FAS). If the number of patients differed by more than 10% between the PPS and the FAS, efficacy analyses based on the PPS for myeloprotection could be performed to support efficacy analyses for the primary and key secondary endpoints.

4.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the duration of severe neutropenia (DSN) during Cycle

1. DSN will be assessed by treatment group using two different strategies. Strategy 1 is the primary analysis and Strategy 2 is the supportive sensitivity analysis. DSN derivation in each strategy will include any unscheduled data and use the actual assessment date (non-visit date).

4.4.1.1. Strategy 1: Missing ANC values not imputed

For patients who experienced at least 1 episode of severe neutropenia (SN) within each cycle, a DSN is defined as the number of days from the date of the first absolute neutrophil count (ANC) value $< 0.5 \times 10^9$/L in that cycle to the date of the first ANC value $\geq 0.5 \times 10^9$/L that met the following requirements: (1) occurred after an ANC value $< 0.5 \times 10^9$/L, and (2) no other ANC value $< 0.5 \times 10^9$/L occurred between that date and the end of that cycle (otherwise the SN event is considered not resolved at the end of that cycle). If a patient does not experience any SN during the cycle, DSN will be counted as 0 for that cycle. Exceptions will be handled using the following rules:

- If the SN event is not resolved at the end of the cycle, the DSN will be calculated as above, but the end date is the end date of the cycle;
- If a patient dies during the period of the SN event, the DSN will be calculated as described above, but the end date is the date of death;
- If a patient withdraws consent or is lost to follow-up during the period of the SN event, the DSN will be calculated as described above, but the end date will be the last ANC assessment date before the end of the study.

Nonparametric analysis of covariance (Nonparametric ANCOVA) will be used to evaluate DSN-based differences in efficacy between the test and placebo groups. The nonparametric covariance model will include covariates of baseline ANC study value as a continuous variable, and fixed effects of number of lines of treatment (1st line versus 2nd/3rd line), ECOG (0 or 1 versus 2), brain metastases (yes versus no), and treatment arm (Trilaciclib versus placebo) as categorical variables. Stratification will be combined or reduced appropriately if the number of patients within a stratum is small. The p-value for the 2-sided test will be calculated from the model, and it will be provided the difference in means between the two treatment groups and its 95% confidence interval (CI) based on Satterthwaite t-test, as well as the median difference between the groups and its 95% confidence interval estimated using Hodges-Lehmann.

In addition, DSN will be summarized for each cycle by treatment group using descriptive statistics.

4.4.1.2. Strategy 2: Missing ANC values not imputed, censored handling unresolved SN

For patients who experienced at least 1 episode of severe neutropenia (SN) within each cycle, a DSN is defined as the number of days from the date of the first absolute neutrophil count (ANC) value < 0.5 x 10^9/L in that cycle to the date of the first ANC value ≥ 0.5 x 10^9/L that meet the following requirements: (1) occurred after an ANC value < 0.5 x 10^9/L, and (2) no other ANC value < 0.5 x 10^9/L occurred between that date and the end of that cycle (otherwise the SN event is considered not resolved at the end of that cycle). Patients will not be included in the analysis if they does not experience any SN during this period. Exceptions will be handled using the following rules:

- If the SN event is not resolved at the end of the cycle, the DSN will be calculated as described above, but the end date will be the end date of the cycle or the last contact date, whichever occurs first;
- If a patient dies, withdraws consent, or is lost to follow-up during the period of the SN event, the DSN will be calculated as described above, but the end date will be the last ANC assessment before the end of the study.

Overall DSN (days) during treatment is the median DSN value for all cycles and the following data handling rules will be applied:

- If a patient 's SN event duration value is censored for all cycles, the patient' s median DSN value will be the median censored value and will be considered censored;
- If a patient 's partial cycle SN time duration value is a censored value, the Kaplan-Meier method will be used to estimate the median DSN value for that patient, which is the observed value;
- If a patient 's median DSN value cannot be calculated (eg, has ≤ 2 DSN values), the longest DSN value across all cycles (whether censored or not) will be used as the median value, but the corresponding censoring flag will be included in the analysis.

Kaplan-Meier methods will be used to estimate 25%, median, and 75% time (days) of the duration of SN and 95% confidence intervals (days) will be provided. Adjusted hazard ratio (HR) and its 95% CI between the two treatments (Trilaciclib versus placebo) will be calculated from a stratified Cox proportional hazard model with treatment group and randomization stratification factors based on Interactive Response Technology (IRT) as fixed effects. Stratification will be combined or reduced appropriately if the number of patients within a stratum is too small. Two-sided p-values will be calculated from stratified log-rank tests.

4.4.2. Key Secondary Efficacy Endpoints

Key secondary efficacy endpoints include the incidence of severe neutropenia (SN), the incidence of red blood cell (RBC) transfusions (occured on/after Week 5), granulocyte colony-stimulating factor (G-CSF) use, and the composite endpoint of major adverse hematologic event (MAHE).

4.4.2.1. Incidence of serious neutropenia events

The total number of SN events is the total number of cycles with at least one ANC value $< 0.5 \times 10^9$/L. For example, two ANC values less than 0.5×10^9/L during Cycle 2 are counted as only one SN event. If a patient does not experience any SN events, the number of SN events for that patient will be counted as zero. Unscheduled data will be included and and actual SN assessment date (non-visit date) will be used. Whether a patient experienced a SN event is a binary variable (yes or no); 'yes' if ≥ 1 cycles with a SN event is observed; and 'no' otherwise.

SN events will be summarized by treatment group using descriptive statistics. Part 2 of the study will analyze the adjusted rate ratio (aRR) between the two treatment groups based on a modified Poisson regression model. The model includes baseline ANC measurement as covariate and IRT-based randomization stratification factors including number of lines of therapy (1st line versus 2nd/3rd line), ECOG (lines 0-1 versus 2) (not included in the actual analysis), and brain metastases (yes versus no), as well as treatment arm as fixed effects. Logarithmic transformed values of the number of cycles will be included in the modeling as offset variables. P-values, aRR (Trilaciclib versus placebo) and their 95% CIs will be provided for the 2-sided tests. In addition, Cochran-Mantel-Haenszel (CMH) weights will be used to calculate the adjusted rate difference between the two arms (Trilaciclib versus placebo) and its 95% CI in Part 2 of the study, and stratified exact CMH method will be used to calculate P values under the 2-sided test according to IRT-based randomization stratification factors to test the stability of the analysis results.

4.4.2.2. Incidence of red blood cell transfusion events occured on/after Week 5

Each red blood cell (RBC) transfusion (including whole blood transfusion and each red blood cell component) occured on/after Week 5 is defined as a separate event and included in the efficacy analysis. Whether a patient experiences a RBC transfusion event is defined as a binary variable (yes or no); "yes" if a total number of RBC transfusion events ≥ 1 is observed, otherwise "no".

The statistical analysis method is similar to that described for SN incidence in Section 4.4.2.1, except hemoglobin (HGB) baseline measurement will be used as covariate instead of

ANC baseline measurement in a modified Poisson regression model. In addition, the offset variables will be log-transformed values for duration of treatment (weeks) rather than cycles.

4.4.2.3. Use rate of granulocyte colony-stimulating factor

Prophylactic use of any prophylactic colony-stimulating factors (including granulocyte colony-stimulating factor G-CSF, granulocyte-giant cell colony-stimulating factor, erythropoietin) is not permitted in principle in Cycle 1, but febrile neutropenia with high-risk infections or risk factors suggestive of poor prognosis is permitted for therapeutic use.

Determine if G-CSF is used in this cycle by comparing the start and end dates of each use of granulocyte colony-stimulating factor (G-CSF) with the start and end dates of the treatment cycle. If the date of G-CSF use lies between the start and end dates of the cycle, the cycle will be considered as having G-CSF use. The total number of events with G-CSF use is the total number of cycles with at least one GCSF administration. If a patient does not take any G-CSF, the number of G-CSF administration events for that patient is zero. Thus, whether a patient experiences an event of G-CSF administration is defined as a binary variable (yes or no); "yes" if the number of cycles with G-CSF administration is ≥ 1 and "no" otherwise.

Statistical analysis method is similar to that for SN incidence described in Section 4.4.2.1.

4.4.2.4. Total occurrence of major adverse hematologic event

Major adverse hematologic event (MAHEs) are composite endpoints to assess the effect of Trilaciclib. MAHE consists of the following 5 component events:

- Involved hospitalization
- Leading to chemotherapy dose reduction
- Febrile neutropenia
- Extended SN (greater than 5 days)
- RBC transfusion occured on/after Week 5.

The total number of events for each MAHE component is the sum of the number of events that occurred on the date of first study drug administration and before the end of the last treatment cycle. The total number of events for MAHEs during treatment is the sum of the number of events for each MAHE component. For patients who does not experience any MAHE, the total number of MAHE events is 0.

MAHEs will be coded using the most current version of MedDRA and the total number of MAHEs, duration of treatment (weeks), weekly event rates, and cumulative event rates every 3 weeks will be summarized by number of lines of treatment. According to the actual MAHEs, the above summaries will be repeated separately by component events , but for MAHE component events leading to chemotherapy dose reduction and SN prolongation, the cumulative

event rates will be summarized by cycle rather than every 3 weeks. Part 2 of the study will also analyze the adjusted rate ratio between the Trilaciclib and placebo groups using a negative binomial regression model. The model includes the three IRT-based randomization stratification factors and treatment group as fixed effects, and the log-transformed values of treatment duration (weeks) or cycle number as offset variables. Two-sided P values, aRR (Trilaciclib versus placebo) and their 95% CIs will be provided. Cumulative incidence of MAHEs within specified subgroups will be presented using forest plots.

Time to first onset (months) for each MAHE component event = (date of first MAHE component event – date of first study drug administration + 1)/30.

For patients who developes MAHEs, the time (months) from the first study drug administration (randomization date in Part II) to the first occurrence of MAHEs will be summarized and Kaplan-Meier curves will be provided. Time to first MAHE refers to the event with the shortest time to first occurrence of the MAHE component; if a patient does not have an MAHE, it will be censored at the end date of the last cycle, date of death, end of study, or last contact date for that patient, whichever cames first.

Kaplan-Meier methods will be used to estimate 25%, median, and 75% time (months) to first MAHE and provide 95% CIs (months). Part 2 of the study calculates the HR and its 95% CI between the two treatments (Trilaciclib versus placebo) from a stratified Cox proportional hazards model with treatment group and IRT-based randomization stratification factors as fixed effects, and 2-sided P values will be calculated from a stratified log-rank test.

4.4.3. Other Secondary Efficacy Endpoints

Descriptive statistics will be used to summarize the following additional secondary efficacy endpoints. Descriptive statistics for continuous data will include means, medians, standard deviations and ranges, and categorical data will provide frequencies and percentages.

4.4.3.1. Absolute neutrophil count trough values by cycle

Absolute neutrophil count (ANC) will be summarized by descriptive statistics for cycle trough values (which are lower than the ANC value at baseline for that cycle) and changes from baseline between the start and end of each cycle. Cycle trough values for ANC will be summarized descriptively for Part II of the study to evaluate confounding effects of G-CSF administration separately by the presence or absence of G-CSF administration during treatment.

4.4.3.2. Absolute neutrophil counts, platelet counts, absolute lymphocyte counts, and hemoglobin over time

Hematology parameters, including ANC, platelet count, absolute lymphocyte count (ALC), and hemoglobin (HGB) will be summarized by treatment group using descriptive statistics

based on laboratory hematology results at baseline and each visit time point. Listing will be provided for detials. ANC will be summarized descriptively to evaluate confounding effects of G-CSF administration separately according to the presence or absence of G-CSF administration during treatment.

Time-line plots for mean ANC, platelet count, ALC, HGB, and change from baseline in HGB (with 95% confidence intervals) will be provided by cycle.

4.4.3.3. Other dichotomous endpoints

The total number of events below is the total number of cycles with at least one event. If a patient does not experience any of the following events during the treatment period, the number of events for that patient is zero. 'Yes' if ≥ 1 of the following events are observed; otherwise 'No'.

- Incidence of Grade 3 and 4 Hematologic Toxicities: Grade 3 and 4 hematologic toxicities refers to hematology laboratory results with CTCAE Grade 3 or 4.
- Incidence of platelet transfusion (during chemotherapy)
- Incidence of febrile neutropenia

Each of the following events with a unique start date will be defined as a separate event during the treatment period. Yes if the total number of the following events observed is ≥ 1, otherwise no.

- Incidence of intravenous or oral antibiotics
- Incidence of infectious serious adverse events
- Incidence of serious adverse events of lung infection

Determine if the following medications is used in that cycle by comparing the start and end dates of each use of the following medications with the start and end dates of the treatment cycle. The total number of events with the following medications is the total number of cycles with at least one dose of the following medication. If a patient did not take the following medications during the treatment period, the number of events for that patient is 0.

- Erythropoiesis-stimulating agent (ESA) Usage
- Recombinant human interleukin-11 (IL-11) use rate
- Thrombopoietin (TPO) use

The total number of events as well as the incidence of the above dichotomous variables will be summarized descriptively and tabulated in detail by patient. The statistical analysis approach is similar to that described for SN incidence in Section 4.4.2.1, except that baseline ANC measurements will not be included as covariates in the modified Poisson regression model.

In addition, for comparing the incidence of antibiotic administration, SAEs of infection, and SAEs of lung infection between the Trialciclib and placebo groups, the offset variable in the modified Poisson regression model will be the log transformed duration of treatment (weeks) rather than the number of cycles.

4.5. Anti-tumor efficacy analysis

4.5.1. Objective tumor response rate and disease control rate

A pooled analysis of objective tumor response rate (ORR) and disease control rate (DCR) assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1) will be performed based on the Response Evaluation Analysis Set (RES). Based on the assessments at each visit, the number and percentage of patients with best response of CR, PR, SD, PD and NE will be summarized by treatment group when CR/PR confirmation is not required and CR/PR confirmation is required, respectively .

ORR is calculated based on the number of patients with best response of CR or PR. DCR is calculated based on the number of patients with best response of CR, PR, or SD, and 95% CIs for ORR and DCR will be calculated using the Clopper-Pearson method.

ORR as a binary endpoint ("yes"or"no"), CMH weights will be used to analyze the difference in adjusted rates between the two treatment arms (Trilaciclib versus placebo) and their 95% CIs, and 2-sided P values will be calculated based on the stratified exact CMH method.

Waterfall plots of best percentage change from baseline in sum of target lesion diameters, time line plots of change from baseline, and swimming plots of drug exposure and efficacy assessments will be provided for patients based on RES. Supportive data listings will also be provided.

4.5.2. Progression Free Survival and Overall Survival Analysis

Exploratory analyses of progression-free survival (PFS) will be performed based on the FAS. PFS is defined as the time from the date of randomization to the first documented radiologically disease progression (according to RECIST1.1) or death due to any cause, whichever occurs first. In the absence of disease progression and death at the time of analysis, PFS will be censored at the date of last tumor assessment; in the absence of a valid postbaseline tumor assessment, PFS will be censored at the date of the date of randomization.

Exploratory analyses of overall survival (OS) will be performed based on the FAS . OS is defined as the time from the date of randomization to death of the patient for any cause; for patients who have not died at the time of analysis, OS will be censored at the date last known to be alive .

PFS and OS rates at various time points will be estimated using the Kaplan-Meier method,

and 95% CI will be provided using Greenwood 's method. The Kaplan-Meier method will also be used to estimate 25%, median, and 75% time (months) for PFS and OS, and the Brookmeyer-Crowley method will be used to calculate the 95% CI and survival curves for PFS and OS will be provided. The HR and its 95% CI will be calculated between the two treatment arms (Trilaciclib versus placebo) based on a stratified Cox proportional hazards model with treatment arm and IRT-based randomization stratification factors as fixed effects. Two-sided P values will be calculated from stratified log-rank test.

4.6. Safety analysis

Safety analyses will be based on SS. Safety evaluations includes adverse events (TEAEs), physical examinations, vital sign measurements, electrocardiograms (ECGs), and laboratory tests (hematology, blood chemistry, and urinalysis) throughout the treatment period.

4.6.1. Extent of Study Drug Exposure

Duration of exposure to study drug during the treatment period and number of treatment cycles started will be summarized using descriptive statistics. Cumulative actual dose, cumulative planned dose, cumulative planned dose for compliance, cumulative planned dose for compliance, medication compliance, and relative dose intensity will be summarized for the different study drugs (Trilaciclib or chemotherapy drugs), respectively.

- Duration of chemotherapy exposure (days) = date of first dose of study drug in last cycle – date of first dose of study drug + 21 days
- Number of treatment cycles

A treatment cycle is considered to be started if the subject receives at least one dose of study drug (Trilaciclib/placebo or chemotherapy). Descriptive statistics will be used to summarize the number of cycles started and to summarize the counts and percentages of subjects by the number of cycles started.

- Relative dose intensity (%) = (cumulative actual dose administered/cumulative planned dose administered) 100%,

If applicable, the proportion of subjects with dose reductions will be summarized separately by study drug. Number of events with dose reductions will be described and the number and percentage of subjects will be summarized by number of dose reductions.

- The dose of Trilaciclib/placebo will not be adjusted in this trial and will remain at 240 mg/m^2 unless safety data in Part 1 suggests that dose adjustment of Trilaciclib/placebo is warranted.
- Carboplatin, etoposide and topology are determined by comparing the actual dose on the

respective dosing pages of the current and previous cycles Dose reductions for ticam are shown in Table 1 for Cycle 2 and Day 1 of subsequent cycles.

Table 1 Dose reductions for carboplatin, etoposide and topotecan

Dose Level	Etoposide (mg/m^2)	Carboplatin AUC	Topotecan (mg/m^2)
Dose Level -1	Reduce to 75	Decreased to AUC = 4	1
Dose Level -2	Reduce to 50	Decreased to AUC = 3	0.8

No more than two dose reductions are allowed (concurrent carboplatin and etoposide dose reductions are one dose reduction), dose reductions are unidirectional permanent, and no dose increases are allowed. Delays in chemotherapy cycles of up to 1 week due to operational reasons such as legal holidays and up to 2 weeks due to treatment toxicity may be permitted; however; If, in the opinion of the investigator, the subject is still benefiting from a dose delay of more than 2 weeks, the investigator requests and obtains the sponsor 's medical care Dosing may be delayed for greater than 2 weeks following review and written approval.

The proportion of subjects with treatment cycle delays and reasons for delays will be summarized separately by study drug as applicable. Number of cycles delayed will be statistically described and the number and percentage of subjects will be summarized by the number of cycles delayed.

4.6.2. Adverse Events

Adverse events will be monitored from the time of informed consent through the end of the safety follow-up period, initiation of new antineoplastic therapy, or withdrawal from the study, whichever comes first. Adverse events will be graded and recorded according to NCI-CTCAE version 5.0 throughout the study and during follow-up.

Only treatment-emergent adverse events (TEAEs) will be summarized. A TEAE is defined as any untoward medical occurrence or an adverse event that worsened relative to pretreatment state that emerged newly from the first dose of study drug through 30 days after the last dose or before the start of new anticancer therapy. AE will be coded according to the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA) and the number and incidence will be summarized by System Organ Class (SOC) and Preferred Term (PT). Serious adverse events after medication, adverse events leading to dose reduction, delay or discontinuation, adverse events leading to dropout, adverse events leading to death, adverse events of special interest, drug-related adverse events, etc. will be summarized separately, and the details of each adverse event for each patient will listed, including the type, severity, occurrence and duration, outcome of adverse events, and the relationship with the

study drug.

For summarizing TEAE, the incidence of adverse events will be calculated based on the number of patients with adverse events rather than the number of adverse events. When calculating the number and percentage of patients with adverse events, one patient with multiple occurrences of the same adverse event will only be counted one.

4.6.3. Clinical Laboratory Tests

Hematology and blood chemistry test results at baseline and each visit time point and corresponding changes from baseline will be summarized descriptively and listing will be provided in detail. CTCAE grades for hematology and blood chemistry will be determined according to the laboratory parameter CTCAE criteria(see Appendix 3). CTCAE Version 5.0 will be used for grading. According to CTCAE Version 5.0, CTCAE grading of some items requires clinical diagnosis or joint judgment of clinical diagnosis and values, which cannot be completely divided by programming, such as hyperglycemia, hypokalemia, hypophosphatemia, hyponatremia and hyperuricemia, CTCAE Version 4.03 will be used for grading. Patients' changes from baseline CTCAE grade to worst postdose CTCAE grade will be summarized using cross-classification tables. Grade 3 or 4 hematology and blood chemistry laboratory abnormalities occurring during treatment will also be summarized separately, as appropriate. Urinalysis results will be presented in listings only.

Actual study days for patients may differ from planned study days between the first dose of study drug in each cycle and the scheduled visit date. In this case, visit-based summaries will categorize assessments based on visit within time window as shown in Appendix 4.

4.6.4. Vital signs

Descriptive statistical summaries and detailed listings of vital sign and changes from baseline at each visit time point will be performed based on vital sign (systolic blood pressure, diastolic blood pressure, respiratory rate, pulse, body temperature, weight, etc.) data values at baseline and each visit time point. Each vital sign is judged for potential clinical relevance according to Table 2 and the number and percentage of patients meeting the criteria will be calculated.

Table 2 Criteria for Vital Signs of Potential Clinical Significance

Parameter	**Criteria for judgment**	**Change from Baseline**
Systolic blood pressure (mmHg)	≥ 180	Increased ≥ 40
	≤ 90	Decline ≥ 40
Diastolic Blood Pressure (mmHg)	≥ 105	Increased ≥ 20
	≤ 50	Decrease ≥ 20

Pulse (bpm*)	≥ 120	Increased ≥ 40
	≤ 50	Decline ≥ 40
Weight (kg)	NA	≥ 10% increase
	NA	≥ 10% decrease

Bpm = beats per minute

4.6.5. ECOG score

Descriptive statistics and detailed listings of ECOG score at each visit and change from baseline will be provided according to ECOG score at baseline and each visit.

4.6.6. Physical examination

Physical examination findings will be presented in listings at baseline and each visit time point.

4.6.7. 12 lead ECG

Descriptive statistics and detailed listings of ECG test results completed at each visit time point and changes from baseline will be provided based on ECG test results at baseline and each visit time point (heart rate, QRS duration, PR, QT, RR and QTc intervals, etc.). Each ECG parameter will be judged for potential clinical relevance according to Table 3 and the number and percentage of patients meeting the criteria will be calculated.

Table 3 Criteria for ECG Parameters of Potential Clinical Significance

Parameter	**Criteria for judgment**
Heart Rate (bpm)	120
	< 50
PR Interval (msec)	≥ 210
RR Interval (msec)	1200
	< 500
QRS interval (msec)	≥ 120
	≤ 50
QT interval (msec)	≥ 500
	≤ 300
QTcB, QTcF Interval (msec)	≥ 500
	≥ 480
	≥ 450
	≤ 300
	≥ 30 change from baseline
	≥ 60 change from baseline

4.7. Analysis time

The primary analysis for Part 2 will be performed at the end of Cycle 1 for all randomized subjects. Will be necessary for Sponsor Personnel are unblinded, but the investigator, subject, and other personnel will remain blinded. Assessments will be based on unblinded data Primary endpoint of bone marrow protective efficacy of Trilaciclib and other applicable secondary or exploratory endpoints.

The second analysis in Part 2 will be performed after all randomized subjects have completed 6 cycles or end of treatment.

The final analysis in Part 2 will be performed at the end of the study.

4.8. Subgroup analysis

Designated efficacy and safety endpoints will be analyzed in the following subgroups as appropriate by treatment group (Trilaciclib vs. placebo) and other subgroup analyses will be performed as needed.

- Number of lines treated (1 lines vs. 2/3 lines)
- ECOG (0 or 1 vs. 2)
- Brain metastases (yes vs. no)

4.9. Sensitivity Analysis

Sensitivity analyses of myeloprotective endpoints by the presence or absence of concurrent G-CSF cycles will be conducted to support the stability of the analysis results based on the FAS set.

The stability of the primary analysis results (Strategy 1) for Cycle 1 DSNs will be checked by Strategy 2. Additional sensitivity analyses will be performed as needed.

4.10. Pharmacokinetic analysis

The population pharmacokinetic analysis in Part 2 will be exploratory based on the data obtained and its analysis plan will be presented in a separate population pharmacokinetic analysis plan.

4.11. Handling of Missing Data

Every effort should be made to minimize the generation of missing data. Missing data will not be imputed unless otherwise specified. For time-to-event endpoints in efficacy, missing data will be handled based on statistical analysis model; for response rate in efficacy (such as ORR, DCR), missing data will be considered as non-responder and included in the analysis.

5. APPENDICES

5.1. Appendix 1 Protocol Synopsis

Title :	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Trilaciclib in Patients with Extensive Stage Small Cell Lung Cancer Treated with Carboplatin and Etoposide or with Topotecan**
Protocol No. :	**B02B00801-TRILA-301**
Protocol Version No.:	**V1.3**
Version Date :	**August 17, 2021**
Sponsor:	**Jiangsu Simcere Pharmaceutical Co., Ltd.**

Study title	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Trilaciclib in Patients with Extensive Stage Small Cell Lung Cancer Treated with Carboplatin and Etoposide or with Topotecan
STUDY PHASE	Phase III
Study objectives	**Part I (Safety Run-in and PK Evaluation Part):** **Primary objective** • To evaluate the pharmacokinetic (PK) profile of Trilaciclib in patients with extensive stage small cell lung cancer; • To evaluate the safety and tolerability of Trilaciclib in patients with extensive stage small cell lung cancer; • To evaluate the effectiveness of Trilaciclib (prevention of chemotherapy-induced myelosuppression) in patients with extensive stage small cell lung cancer; **Secondary objectives** • To comprehensively evaluate the myeloprotective effect of Trilaciclib in patients with extensive stage small cell lung cancer; • To evaluate the short-term antitumor efficacy of Trilaciclib in patients with extensive stage small cell lung cancer; **Exploratory objectives:** • To evaluate the long-term antitumor efficacy of Trilaciclib in patients with extensive stage small cell lung cancer; • Population pharmacokinetic profile. **Part II (randomized, double-blind part):**

	Primary objective • To evaluate the effectiveness of Trilaciclib (prevention of chemotherapy-induced myelosuppression) in patients with extensive stage small cell lung cancer; **Secondary objectives** • To comprehensively evaluate the myeloprotective effect of Trilaciclib in patients with extensive stage small cell lung cancer; • To evaluate the safety and tolerability of Trilaciclib in patients with extensive stage small cell lung cancer; • To evaluate the short-term antitumor efficacy of Trilaciclib in patients with extensive stage small cell lung cancer; **Exploratory objectives:** • To evaluate the long-term antitumor efficacy of Trilaciclib in patients with extensive stage small cell lung cancer; • Population pharmacokinetic profile.
Study Endpoints	The following endpoints, not specified, refer to events occurring during chemotherapy. **Part I (Safety Run-in and PK Evaluation Part):** Primary Endpoint: • PK profile (C_{max}, AUC and other PK parameters); • Safety and tolerability: adverse events, laboratory abnormalities, etc; • Duration of severe neutropenia in Cycle 1 (DSN); Key Secondary Endpoints: • Occurrence of severe neutropenia (SN); • Occurrence of red blood cell transfusion (on/after Week 5); • Granulocyte colony stimulating factor (G-CSF) use rate; • Composite endpoint – major adverse hematologic event (Any of the following): ■ All-cause hospitalization; ■ All-cause dose reductions; ■ Febrile neutropenia; ■ SN prolongation (lasting > 5 days); ■ Red blood cell (RBC) transfusions were performed on/after Week 5. Other secondary endpoints: • Occurrence of Grade 3 and 4 hematological toxicities; • Absolute neutrophil count trough by cycle; • Absolute neutrophil count, platelet count, absolute lymphocyte count, and hemoglobin over time; • Erythropoiesis stimulating agent (ESA) utilization rate;

	• Rate of recombinant human interleukin-11 use; • Thrombopoietin (TPO) use rate; • Occurrence of intravenous or oral antibiotic administration; • Occurrence of infectious serious adverse events; • Occurrence of lung infection SAEs: • Occurrence of febrile neutropenia; • Occurrence of platelet transfusion; • Objective tumor response rate (ORR); • Disease control rate (DCR). **Exploratory Endpoints:** • Progression-free survival (PFS); • Overall survival (OS); • Population pharmacokinetic profile. **Part II (randomized, double-blind part):** Primary Endpoint: • Duration of severe neutropenia in Cycle 1 (DSN). Key Secondary Endpoints: • Occurrence of severe neutropenia (SN); • Occurrence of red blood cell transfusion (on/after Week 5); • Granulocyte colony stimulating factor (G-CSF) use rate; • Composite endpoint – major adverse hematologic event (Any of the following): ▪ All-cause hospitalization; ▪ All-cause dose reductions; ▪ Febrile neutropenia; ▪ SN prolongation (lasting > 5 days); ▪ Red blood cell (RBC) transfusions were performed on/after Week 5. Other secondary endpoints: • Occurrence of Grade 3 and 4 hematological toxicities; • Absolute neutrophil count trough by cycle; • Absolute neutrophil count, platelet count, absolute lymphocyte count (ALC), and hemoglobin over time; • Erythropoiesis stimulating agent (ESA) utilization rate; • Rate of recombinant human interleukin-11 use; • Thrombopoietin (TPO) use rate; • Occurrence of intravenous or oral antibiotic administration; • Occurrence of infectious serious adverse events; • Occurrence of lung infection SAEs:

	• Occurrence of febrile neutropenia; • Occurrence of platelet transfusion; • Safety and tolerability: adverse events, laboratory abnormalities, etc.; • Objective tumor response rate (ORR); • Disease control rate (DCR). **Exploratory Endpoints:** • Progression-free survival (PFS); • Overall survival (OS); • Population pharmacokinetic profile.
BACKGROUND AND RATIONALE	Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers, and approximately 70% of these patients are in the extensive stage at initial diagnosis. Major diagnosis and treatment guidelines at home and abroad (including those edited by Chinese Society of Clinical Oncology) recommend platinum-based combination with or without PD-L1 antibody as first-line standard treatment for SCLC, while topotecan is recommended for second-line chemotherapy. Studies have shown that platinum-based combination therapy with etoposide or topotecan is associated with significant myelosuppression in extensive stage SCLC (neutropenia 47% to 92%, leukopenia 8% to 66%, thrombocytopenia 10% to 46%, and anemia 7% to 34%). In Asian populations (including China, Korea, Japan), the occurrence of myelosuppression caused by platinum-based and etoposide chemotherapy was similar. Literature have shown that chemotherapy-induced myelosuppression (grade 3/4 neutropenia 5.6% ~ 93.8%, anemia 2.9% ~ 33.3%, thrombocytopenia 3.2% ~ 33.3%) is always the main adverse reaction to be urgently addressed in Asian populations, including China, South Korea, and Japan, for patients with small cell lung cancer treated with carboplatin/cisplatin combined with etoposide effects or topotecan. Myelosuppression is an important cause of many adverse events in cancer chemotherapy, such as infection, sepsis, bleeding, and fatigue, leading to hospitalization or the use of hematopoietic growth factors or the need for red blood cell and/or platelet transfusions. In addition, myelosuppression often leads to chemotherapy dose reductions or limits in treatment dose intensity, rendering patients unable to derive greater benefit from chemotherapy. Trilaciclib is a highly potent, selective, reversible CDK4/6 inhibitor in clinical development to protect bone marrow by protecting hematopoietic stem and progenitor cells (HSPCs) when administered systemically. The proliferation and differentiation of HSPCs is very dependent on CDK4/6 activity and is arrested in G1 phase of the cell cycle when exposed to appropriate doses of Trilaciclib, thus avoiding damage by cytotoxic chemotherapeutic agents of the cell cycle. Therefore, for CDK4/6-independent tumors (such as small cell lung cancer, etc.), Trilaciclib

	combined with chemotherapy can protect the bone marrow without antagonizing the anti-tumor efficacy of chemotherapy. The downstream target of CDK4/6 is the retinoblastoma (Rb) protein, which is phosphorylated upon CDK4/6 activation to allow cells to enter S phase. CDK4/6 inhibitors arrest cells in G1 phase by inhibiting downstream pathways dependent on functional Rb protein. It has been shown that SCLC is universally inactivated by tumor protein-53 (TP53) and retinoblastoma protein-1 (RB-1), so it is basically believed that functional Rb protein is almost absent in SCLC. In addition, two recent reports have described the genomic profile of SCLC in detail using next generation sequencing methods, including complete exome sequencing, transcriptome profiling by RNA sequencing (RNASeq), copy number analysis as well as limited whole genome sequencing to identify translocations. These reports confirm the conjecture raised in previous studies based on small numbers of tumor samples that inactivation of driver mutations TP53 and RB-1 commonly occurring in SCLC. Consistent with these findings, preclinical in vitro and in vivo studies have shown that Trilaciclib administered prior to chemotherapy does not attenuate the killing of RB-1 inactive tumors, including SCLC. Thus, SCLC can be considered CDK4/6-independent due to near universal RB-1 inactivation, which makes selective protection of HSPCs without compromising the antitumor efficacy of chemotherapy a potentially viable therapeutic strategy. Three randomized, double-blind Phase 2 clinical trials in patients with small cell lung cancer (SCLC) demonstrated that Trilaciclib administered in combination with chemotherapy (including 1st line, 2nd/3rd line) prevented or mitigated chemotherapy-induced myelosuppression. The G1T28-05 and G1T28-02 studies showed that Trilaciclib administered before first-line chemotherapy (carboplatin combined with etoposide) reduced the duration of severe neutropenia in Cycle 1 from 4 days and 3 days to 0 days, and the occurrence of severe neutropenia from 49.1% and 42.1% to 1.9% and 5.1%, respectively; the G1T28-03 study results showed that the use of Trilaciclib before topotecan reduced the duration of severe neutropenia in Cycle 1 from 7 days to 2 days, and the occurrence of severe neutropenia from 75.9% to 40.6%. Currently, no therapies have been approved for improving myelosuppression caused by chemotherapy by protecting HSPCs. Although there are some symptomatic treatments for myelosuppression (e.g., blood transfusions, growth factors, etc.), there are no available treatments that provide patients with comprehensive protection from chemotherapy-induced damage to HSPCs and the resulting negative effects. As the first agent designed to reduce chemotherapy-induced myelosuppression by protecting HSPCs, Trilaciclib showed significant

	ability to prevent or alleviate chemotherapy-mediated myelosuppression in the multicellular lineage in patients with extensive stage small cell lung cancer (ES-SCLC). Based on the clinical data of Trilaciclib, we intend to conduct a clinical trial in China that includes an open-label safety run-in and PK evaluation part and a randomized double-blind, placebo-controlled efficacy validation part to assess the safety, efficacy and pharmacokinetics of Trilaciclib in combination with carboplatin and etoposide (EC regimen) or with topotecan in the treatment of extensive-stage non-small cell lung cancer.
Study Design	This is a multi-center Phase 3 clinical trial with an open-label single-arm safety run-in and PK evaluation part and a randomized double-blind, placebo-controlled part in patients with ES-SCLC to evaluate the safety, efficacy, and pharmacokinetic profile of Trilaciclib based on completed clinical studies abroad. The study consists of 2 parts. The first part, safety run-in and PK evaluation, enrolled approximately 12 patients with extensive-stage small-cell lung cancer, 6 patients each with 1st line ES-SCLC and 2nd/3rd line ES-SCLC to receive Trilaciclib in combination with carboplatin and etoposide (EC regimen) or with topotecan, and based on evaluable data from Cycle 1, evaluated the safety, tolerability, pharmacokinetics, and preliminary efficacy (prevention of myelosuppression) of Trilaciclib. The second part is a randomized double-blind, placebo-controlled efficacy validation study, and approximately 80 patients with ES-SCLC will be enrolled in Part II, stratified by 1st line vs 2nd/3rd line ES-SCLC, ECOG PS (0-1 vs 2), and presence vs absence of brain metastases, and randomized in a 1:1 ratio to Trilaciclib and placebo, in which patients with 1st line ES-SCLC receive Trilaciclib/placebo combined with EC regimen (Trilaciclib-EC group and placebo-EC group), and patients with 2nd/3rd line ES-SCLC receive Trilaciclib/placebo combined with topotecan (Trilaciclib-TPT group and placebo-TPT group), and the efficacy of Trilaciclib (prevention of myelosuppression) will be evaluated with duration of severe neutropenia (DSN) in Cycle 1 as the primary endpoint. The planned dose of Trilaciclib is 240 mg/m^2. If the safety data from the first part of the study suggest that the dose of Trilaciclib needs to be adjusted, 12 additional patients (6 patients each for 1st line ES-SCLC and 2nd/3rd line ES-SCLC) will be enrolled in the first part of the study to explore the PK and safety of Trilaciclib 200 mg/m^2. The study process includes screening period, treatment period, safety follow-up and survival follow-up. The end of the study is defined as death in 75% of subjects, or 12 months after the last subject is enrolled, or the sponsor decided to terminate the study, whichever came first.

Investigational drug	Investigational product investigated: Trilaciclib: Jiangsu Simcere Pharmaceutical Co., Ltd., 300 mg/vial, lyophilized powder Trilaciclib placebo: The outer packaging box of placebo is designed to be consistent with the investigational drug Trilaciclib, and the contents of the box were fillers (disks) of the same quality, which did not break the blind by appearance and hand after sealing. Background Therapy/Chemotherapy: Carboplatin: Qilu Pharmaceutical Co., Ltd., 100 mg/10ml/box, solution Etoposide: Jiangsu Hengrui Medicine, 100 mg/5ml/vial, solution Topotecan: Jiangsu Aosaikang Pharmaceutical Co., Ltd., 2 mg/vial, solution
Study treatment	**Chemotherapy**: Carboplatin - administered on Day 1 of each 21-day cycle at a target AUC of 5 (maximum dose 750 mg calculated according to Calvert formula) over 30 min by intravenous infusion; etoposide - administered on Days 1, 2, and 3 of each 21-day cycle at 100 mg/m^2 over 60 min by intravenous infusion; topotecan - administered on Days 1-5 of each 21-day cycle at 1.25 mg/m^2 over 30 min by intravenous infusion. **Trilacicilb or placebo:** Patients receiving chemotherapy regimen of carboplatin combined etoposide: administered at 240 mg/m^2 on Days 1, 2 and 3 of each 21-day cycle prior to chemotherapy using 5% glucose injection or normal saline 250 mL solution, 30 min intravenous drip (try to complete the drip within 30 + 5 min due to PK study). Patients whose chemotherapy regimen is topotecan: every 21 days as a cycle, on Days 1-5 of each cycle as per 240 mg/m^2 was administered before chemotherapy and prepared into 250 mL solution with 5% glucose injection or normal saline and intravenously infused over 30 min (Because it involved PK studies, try to complete the infusion within 30+5 min). Patients with 1st line ES-SCLC received up to 6 cycles of Trilaciclib or placebo combined with carboplatin and etoposide or continued treatment until disease progression, intolerability, withdrawal of consent, or investigator termination, whichever came first; patients with 2nd/3rd line ES-SCLC received Trilaciclib or placebo combined with topotecan until disease progression, intolerability, withdrawal of consent, or investigator termination of treatment, whichever came first. **Notes:** Trilaciclib or placebo should be administered no more than 28 hours apart between infusions for 3 or 5 consecutive days, and no more than 4 hours apart

	between infusions of Trilaciclib and its subsequent chemotherapeutic agents injected (with carboplatin and etoposide, or with topotecan). Trilaciclib or placebo should be administered in combination with chemotherapy, ie, if EC regimen or topotecan is suspended or discontinued, then Trilaciclib or placebo should also be suspended or discontinued. Similarly, subsequent chemotherapy should not be administered in any cycle if the planned administration of Trilaciclib, i.e. Trilaciclib or placebo, has not been completed. Prophylactic use of any colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte-giant cell colony-stimulating factor, erythropoiesis stimulating agent) is not permitted during Cycle 1, but could be used therapeutically if febrile neutropenia developed in patients with high-risk infections or risk factors indicating poor prognosis (sepsis, age > 65 years, neutrophils < 0.1 × 10^9/L, expected neutropenia lasting > 10 days, pneumonia, invasive fungal infections, other clinically documented infections, fever requiring hospitalization, previous febrile neutropenia, etc.).
Study Population	**Criteria for inclusion** Patients must meet all of the following inclusion criteria to be enrolled in the study: 1. Age ≥ 18 years, male or female; 2. Histologically or cytologically confirmed extensive stage small cell lung cancer (ES-SCLC): • Patients scheduled to receive carboplatin plus etoposide regimen: no prior systemic therapy (eg, chemotherapy or combined with immunotherapy); • Patients scheduled to receive topotecan regimen: previously received 1/2 lines of chemotherapy or combined immunotherapy but not topotecan. 3. Presence of at least one radiation-naïve measurable lesion according to RECIST 1.1 criteria; 4. Hemoglobin ≥ 90 g/L; 5. Neutrophil count ≥ 1.5 x 10^9/L; 6. Platelet count ≥ 100 × 10^9/L; 7. Creatinine ≤ 15 mg/L or creatinine clearance (CrCl) ≥ 60 mL/min (Cockcroft-Gault formula); 8. Total bilirubin ≤ 1.5 × upper limit of normal (ULN); 9. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN or ≤ 5 × ULN (for patients with liver metastases); 10. Albumin ≥ 30 g/L; 11. ECOG PS score 0 - 2; 12. Expected survival time ≥ 3 months; 13. Contraception:

	Females: All females of childbearing potential must have a negative serum pregnancy test at screening and must use reliable contraception from signing of informed consent through 3 months after the last dose; Male: Female partners of childbearing potential must use reliable contraception from signing the informed consent until 3 months after the last dose. 14. Understand and sign informed consent. **Exclusion Criteria** 1. Symptomatic brain metastases requiring local radiotherapy or hormonal therapy; 2. History of other malignancies, with the following exceptions: (1) clinically cured cutaneous basal cell or squamous cell tumors; (2) cured a) cervical cancer, b) prostate cancer, c) superficial bladder cancer; or (3) other solid tumors with a clinical cure time of more than 3 years; 3. Uncontrolled ischemic heart disease or clinically significant congestive heart failure (NYHA Class III or IV); 4. Stroke or cardiovascular or cerebrovascular event within 6 months prior to enrollment; 5. Severe active infection; 6. Psychological or other social factors causing insufficient trial compliance; 7. Other uncontrolled serious chronic diseases or conditions that, in the opinion of the investigator, would make participation in the trial inappropriate; 8. Known HIV infection, active hepatitis B (defined as positive HBV DNA), and hepatitis C (positive HCV RNA); 9. Radiation therapy within 2 weeks prior to enrollment; 10. Patients who have received cytotoxic drug therapy or investigational drug therapy within 4 weeks before enrollment, or non-cytotoxic anti-tumor drug therapy within 2 weeks; 11. Subjects in the first part of the study should not take strong or moderate inducers of CYP3A4 concomitantly within 4 weeks before taking the study drug, and strong inhibitors of CYP3A4 concomitantly within 2 weeks before taking the study drug; 12. Toxicity from prior anticancer therapy has not recovered to Grade 0 or 1 (except alopecia); 13. Hypersensitivity to the study drug (Trilaciclib, etoposide, carboplatin, topotecan) or components thereof; 14. Persons who are unable to act independently due to legal restriction or legal sense; 15. Pregnant or lactating women;

	16. Not suitable for participating in this study in the investigator 's opinion.
Pharmacokinetic evaluation	In the first part of this study, PK blood samples will be collected at the following time points. **When the chemotherapy regimen is carboplatin combined with etoposide:** Cycle 1 Day 1: Within 0.5 h before the start of the first Trilaciclib infusion, immediately after the end of infusion (± 2 min, at the end of administration, excluding the flushing time, the same below), and 0.5 h ± 2 min, 1 h ± 5 min, 2 h ± 5 min, 4 h ± 5 min, 6 h ± 5 min, 8 h ± 5 min, and 12 h ± 10 min after the end of infusion. Cycle 1 Day 2: Within 0.5 hours prior to the second Trilaciclib dose (24 hours ± 30 min after the end of the first Trilaciclib infusion). Cycle 1 Day 3: Within 0.5 h before the start of the third Trilaciclib dose, immediately after the end of infusion (± 2 min, excluding flushing time), and 0.5 h ± 2 min, 1 h ± 5 min, 2 h ± 5 min, 4 h ± 5 min, 6 h ± 5 min, 8 h ± 5 min, and 12 h ± 10 min after the end of infusion. Cycle 1 Day 4: 24 h ± 30 min after the end of the third Trilaciclib infusion. A total of 20 blood sampling points, venous blood is collected to determine the concentration of Trilaciclib in blood samples, and pharmacokinetic analysis is performed based on the test results. **When the chemotherapy regimen is topotecan:** Cycle 1 Day 1: Within 0.5 h before the start of the first Trilaciclib dose, immediately after the end of infusion (± 2 min, excluding flushing time), and 0.5 h ± 2 min, 1 h ± 5 min, 2 h ± 5 min, 4 h ± 5 min, 6 h ± 5 min, 8 h ± 5 min, and 12 h ± 10 min after the end of infusion. Cycle 1 Day 2: Within 0.5 hours prior to the second Trilaciclib dose (24 hours ± 30 min after the end of the first Trilaciclib infusion). Cycle 1 Day 3: Within 0.5 hours prior to the third Trilaciclib dose. Cycle 1 Day 4: Within 0.5 hours prior to the fourth Trilaciclib dose. Cycle 1 Day 5: Within 0.5 h before the start of the fifth Trilaciclib dose, immediately after the end of

	infusion (± 2 min, excluding flushing time), and 0.5 h ± 2 min, 1 h ± 5 min, 2 h ± 5 min, 4 h ± 5 min, 6 h ± 5 min, 8 h ± 5 min, and 12 h ± 10 min after the end of infusion. Cycle 1 Day 6: 24 h ± 30 min after the end of the fifth Trilaciclib infusion. A total of 22 blood sampling points, venous blood is collected to determine the concentration of Trilaciclib in blood samples, and pharmacokinetic analysis is performed based on the test results. In the second part of this study, PK blood sample collection is planned at the following time points, and the actual blood collection points could be adjusted according to the pharmacokinetic study results in the first part. For all subjects, venous blood is collected at 4 blood sampling points on Cycle 1 Day 1 at (excluding flushing time) ± 5 min immediately after the end of Trilaciclib/placebo infusion (excluding flushing time), 0.5 h ± 10 min, 5 h ± 1 h after the end of infusion and within 1 h before Trilaciclib/placebo administration on Cycle 1 Day 2 to determine the concentration of Trilaciclib in blood samples, and pharmacokinetic analysis is performed according to the test results.
Safety evaluation	Safety is evaluated by adverse events (adverse events graded using NCI-CTCAE version 5.0), laboratory tests, vital signs, physical examinations, and electrocardiograms.
Efficacy evaluation	Effectiveness refers to prevention of chemotherapy induced bone marrow suppression. Efficacy assessments will be based on: dynamic changes in complete blood counts; hematological toxicities, including febrile neutropenia and related infections; red blood cell and platelet transfusions; hematopoietic growth factor use; systemic antibiotic use; dose reduction and discontinuation of chemotherapy. The study primarily selected the duration of severe neutropenia (DSN) in Cycle 1 as the primary endpoint for efficacy evaluation. The overall protective effect of Trilaciclib on multilineage of bone marrow will also be comprehensively assessed through the evaluation of secondary endpoints, particularly key secondary endpoints (including SN occurrence, occurrence of red blood cell transfusions on/after Week 5, granulocyte colony-stimulating factor use rate, composite endpoint–major adverse hematologic event, etc.).
Antitumor efficacy evaluation	Tumor imaging evaluation is performed according to RECIST1.1. Baseline imaging is performed within 21 days prior to the first dose, every 6 ± 1 week after the first dose, or more frequently if clinically indicated. Imaging examinations should follow calendar days and should not be modified for treatment delays or terminations, and subjects who discontinue study drug for unacceptable toxicity or other reasons other than disease progression should continue to be followed for tumor assessments until disease progression, receipt of new antineoplastic therapy, withdrawal from the

	study, or death, whichever occurs first. Efficacy assessments were classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Confirmation of response according to RECIST 1.1 should be performed no less than 4 weeks from the date of the first documented partial response (PR) or complete response (CR). Imaging assessments for efficacy confirmation may be performed 4 weeks after response is first observed or at the next scheduled imaging time point.
Criteria for Discontinuation of Study Treatment	A subject should discontinue study treatment if any of the following occur: 1. Disease progression, except for subjects who, in the investigator 's judgment, still benefit from the study (e.g., pseudoprogression); 2. To reach the maximum treatment time specified in the protocol; 3. Subject is pregnant; 4. Poor compliance of subjects, such as failure to receive medication and examinations as required, failure to comply with the restrictions on lifestyle during the study, and use of other prohibited concomitant medications, which have a significant impact on the evaluation of study drugs; 5. Initiation of new anticancer therapy; 6. Occurrence of an adverse event that, in the judgment of the investigator, makes it inappropriate to continue treatment with study drug; 7. The investigator considers that study treatment should be discontinued in the best benefit of the subject; 8. The subject or his/her legal representative (only applicable if the subject is not fully capable of civil conduct) requests termination of treatment. Subjects who discontinue study treatment should complete the items specified in the trial flow chart and continue to be followed up according to the protocol.
Criteria for early withdrawal	Subjects could withdraw from the study at any time for any reason. The investigator may decide whether or not to withdraw a subject from the study based on actual clinical circumstances. Criteria for early withdrawal from the study were: 1. Withdrawal of consent by the subject or his/her legal representative (only applicable if the subject himself/herself does not have full civil capacity); 2. Subject lost to follow-up. Subjects who withdrew early were not to undergo any subsequent follow-up and assessments.
Criteria for early termination of the study	The study may be terminated prematurely at any time if agreed to by the investigator and the sponsor in the best benefit of the subject and for reasonable medical or ethical reasons. During termination, the sponsor and investigator will ensure that adequate consideration is given to protecting the subject 's interests. Criteria for early termination of this study were:

	1. Significant safety risk for the study drug in the opinion of regulatory authorities, ethics committees, sponsors or investigators; 2. Identify major defects in the study protocol, or major deviations or human errors during the implementation of the study, which seriously affect the quality of the trial and make it difficult to achieve the purpose of the study; 3. The sponsor may terminate the study for any scientific, medical or ethical reason, but shall fully consider the rights, safety and health of the enrolled subjects; 4. Other reasons that, in the judgment of the sponsor or investigator, make continuation of the study inappropriate.
Sample Size	A total of approximately 92 subjects are planned to be enrolled, including approximately 12 subjects in Part I and 80 subjects in Part II.
Statistical Analysis	**DETERMINATION OF SAMPLE SIZE** The study consists of 2 parts and a total of approximately 92 ES-SCLC patients are planned to be enrolled. The first part (safety run-in and PK evaluation) planned to enroll approximately 6 patients each for 1st line ES-SCLC and 2nd/3rd line ES-SCLC. The second part (efficacy verification) planned to enroll approximately 80 patients with ES-SCLC, stratified by 1st line vs 2nd/3rd line ES-SCLC, ECOG PS (0-1 vs 2), and presence vs absence of brain metastases, to be randomized in a 1:1 ratio to Trilaciclib versus placebo. The sample size for Part I is not based on statistical calculations, but to support PK evaluation and safety run-in. In addition, assuming a 5.3% occurrence of severe neutropenia, there is an approximately 28% probability of developing at least one severe neutropenia in 6 patients; if the occurrenceof severe neutropenia is 40.6%, then the probability is 96% to detect at least one subject occurring severe neutropenia. The sample size of the second part needs to meet the need to test the efficacy of DSNs in Cycle 1 and is calculated by stochastic simulation. An integrated analysis of the three overseas pivotal studies of Trilaciclib in SCLC showed an approximately 4-day reduction in Cycle 1 DSN in the Trilaciclib group compared to the placebo group. Taking into account the derivation of DSN in Cycle 1, DSN in Cycle 1 is 0 if the subject did not experience any SN during Cycle 1. When there is a large proportion of zero-values, i.e., a large proportion of subjects who do not have any SNs in Cycle 1, DSN in Cycle 1more closely follow a Poisson distribution with a mean of -log (proportion of subjects who do not have any SNs in Cycle 1). In the integrated analysis, the proportion of subjects who developed SN during Cycle 1 is 6.7% in the Trilaciclib group compared to 49.6% in the placebo group. Assuming that the proportion of subjects in this study who occurred SN during Cycle 1 is 10% in the Trilaciclib group and 45% in the placebo group, the means of Poisson distributions is 0.105 and 0.598 for the corresponding Trilaciclib and placebo groups, respectively.

	The stochastic simulation is repeated 10,000 times, each time obtaining the DSN in Cycle 1 from a Poiss on distribution and performing comparison between groups by Mann-Whitney-Wilcoxon test, 70 subjects (35 per group) provided approximately 95% power at the test level of $\alpha = 0.05$ (2-sided). Assuming a dropout rate of approximately 12%, the sample size for Part II is 80 subjects (40 per group). **Statistical Analysis** **Part I** The first part will describe its PK profile and evaluate its safety and tolerability based on Cycle 1 data. In addition, preliminary efficacy (prevention of myelosuppression) data will be summarized. **Part II** The second part is mainly to verify the effectiveness of Trilaciclib treatment (prevention of bone marrow suppression). The primary endpoint is duration of severe neutropenia (DSN) in Cycle 1. For subjects who experienced at least 1 episode of severe neutropenia (SN) in Cycle 1, DSN in Cycle 1 is defined as the number of days from the date of the first ANC value $< 0.5 \times 10^9$/L in Cycle 1 to the date of the first ANC value $\geq 0.5 \times 10^9$/L. Where the date of the first ANC value $\geq 0.5 \times 10^9$/L met the following requirements: (1) occurred after the ANC value is $< 0.5 \times 10^9$/L, and (2) there are no other ANC values $< 0.5 \times 10^9$/L between this date and the end of Cycle 1 (otherwise, if this subject entered Cycle 2, it is counted as Day 1 of Cycle 2). If the subject did not experience any SN during Cycle 1, DSN in Cycle 1 is scored as 0. Nonparametric analysis of covariance (Nonparametric ANCOVA) will be used to evaluate the efficacy of DSN in Cycle 1. Mean differences between treatment groups, standard errors, and their 95% confidence intervals based on Satterthwaite t tests will also be provided. Key secondary efficacy endpoints included SN occurrence, occurrence of red blood cell transfusions (on/after Week 5), granulocyte colony-stimulating factor (G-CSF) use, composite endpoints–major hematological adverse events, etc. Descriptive statistics including mean, median, standard deviation and range will be used for continuous data while frequency and proportion will be provided for categorical data. Differences between groups and their 95% confidence intervals will be estimated. Other secondary efficacy endpoints included the occurrence of Grade 3/4 anemia, trough absolute neutrophil count by cycle, absolute neutrophil count, platelet count, absolute lymphocyte count, and hemoglobin over time, occurrence of ESA use, occurrence of recombinant human interleukin-11 use, occurrence of thrombopoietin (TPO) use, occurrence of intravenous or oral antibiotics, occurrence of serious infectious adverse events, occurrence of serious pulmonary infection adverse events, occurrence of febrile neutropenia, occurrence of platelet transfusions

	(during chemotherapy), objective tumor response rate (ORR), and disease control rate (DCR). Descriptive statistics will be used for summaries. Descriptive statistics for continuous data will include means, medians, standard deviations and ranges, and categorical data will provide counts and percentages. **Safety analysis** Safety analyses will be based on the Safety Analysis Set. Descriptive analysis and summary will be performed for adverse events, laboratory test indicators, vital signs and ECG. Occurrence of treatment-emergent adverse events will be provided and summarized by severity and relationship to study drug. **Pharmacokinetic analysis** The first part of the pharmacokinetic analysis included PK concentration analysis and PK parameter analysis. PK concentration analysis: PK concentration data will be summarized and listed by treatment group according to each scheduled sampling time point as defined in the protocol. Mean and median drug concentration-time profiles (linear and semi-log plots) are also plotted. Individual PK concentration data from subjects will be plotted (linear and semi-log plots) against drug concentration versus time by treatment group and analyte according to actual sampling time. Statistical analysis of PK concentrations will be based on the PK Analysis Set. PK Parameter Analysis: Statistical analysis of PK parameters will be summarized descriptively based on the PK Analysis Set. Population pharmacokinetic analyses will be exploratory based on the data obtained. **Data Analysis Time** An analysis will be performed when subjects in Part I have completed Cycle 1 safety and PK assessments. Based on the Cycle 1 data, their PK profiles are characterized and their safety and tolerability are evaluated. In addition, preliminary myeloprotective efficacy (prevention of chemotherapy-induced myelosuppression) data will be summarized. The data of subjects in Part I may be updated synchronously until the end of the study at the time of data analysis in Part II. The primary analysis will be performed at the end of Cycle 1 for all randomized subjects in Part II. The sponsor 's necessary personnel will be unblinded, but the investigators, subjects, and other personnels will remain blinded. The primary endpoint for assessing the myeloprotective efficacy of Trilaciclib, duration of severe neutropenia (DSN) in Cycle 1, as well as other applicable secondary or exploratory endpoints, will be analyzed based on unblinded data. The second analysis in Part II will be performed after all randomized subjects have completed 6 cycles or end of treatment.

	The final analysis in Part II will be performed at the end of the study.

5.2. Appendix 2 Test Flow Sheet

Line 1 ES-SCLC Patient Study Flow (EC Protocol)

	Screening Period	Treatment Period [a] (21 days per cycle, 6 cycles)										Safety Visit [b]	Survival Follow-up [c]
		Cycle 1						Cycle 2 and above					
	D-21 ~ -1	D1	D2	D3	D8	D10	D15	D1	D2	D3	D8	+ 30 days	Every 60 days
Window (Days)					± 1	± 1	± 1	± 3			± 1	± 7	± 7
Informed Consent	X												
Demographic information	X												
Past medical history [d]	X												
Checked in/out	X												
Randomization (Part II only)	X												
ECOG	X	X						X				X	
Physical examination	X				X		X	X				X	
Body height [e]	X	X						X					
Vital signs	X				X			X				X	
Biochemistry [f]	X				X		X	X			X	X	
Hematology [g]	X	X		X	X	X	X	X			X	X	
Urine test [h]	X							X			X	X	
12-lead ECG	X							X				X	
Serum Pregnancy [i]	X												
Tumor assessment [j]	X	Imaging every 6 ± 1 week after first study drug dose											
PK (Part I) [k]		Part I D1-4 Blood sampling											

	Screening Period	Treatment Period [a] (21 days per cycle, 6 cycles)										Safety Visit [b]	Survival Follow-up [c]
		Cycle 1						Cycle 2 and above					
	D-21 ~ -1	D1	D2	D3	D8	D10	D15	D1	D2	D3	D8	+ 30 days	Every 60 days
Window (Days)					± 1	± 1	± 1	± 3			± 1	± 7	± 7
PK (Part II) [k]		Part II Day 1-2 Blood sampling											
Trilaciclib/Placebo [l]		X	X	X				X	X	X			
Carboplatin [l]		X						X					
Etoposide [l]		X	X	X				X	X	X			
Virology [m]	X												
AEs	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Survival and other anti-tumor conditions													X

a. Trilaciclib + EC chemotherapy will be administered in 21-day cycles until disease progression, intolerability, or discontinuation of treatment at the investigator 's discretion (eg, 6 cycles of chemotherapy have been completed).

b. Follow-up was performed 30 days (± 7 days) after the last dose, starting a new anticancer therapy (-7 days), or withdrawing from the study (-7 days), whichever came first.

c. Survival follow-up refers to telephone follow-up every 60 days (± 7 days) after the last dose to collect other anti-tumor information until 50% of subjects die.

d. Smoking history, family history and relevant medical history of tumor diagnosis and treatment should be collected for medical history; symptoms, signs, laboratory abnormalities within 4 weeks before signing the informed consent form, medication history within 14 days before signing the informed consent form, and weight change within 6 months (> or < 5%). Results of examinations performed at our hospital within 21 days prior to the first dose (Part I) or randomization (Part II) and meeting the requirements of this protocol prior to signing of informed consent (hematology, biochemistry, and urinalysis should be performed within 7 days prior to the first dose of each trial part, pregnancy should be performed within 21 days prior to the first dose of each trial part, and virology and pregnancy tests may be performed outside hospital) can be used for screening assessments without the need for the same tests during the screening period. Patients who fail the initial screening may not be rescreened (only once) until consultation with the Sponsor 's designated medical representative and approval by the Sponsor.

e. Height will be measured only at Screening and weight will be measured pre-dose every cycle except Screening.

f. Biochemistry tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GT), lactate dehydrogenase (LDH), cholesterol (TC), triglyceride (TG), total bilirubin (TBIL), direct bilirubin (DBIL), total protein (TP), albumin (ALB), alkaline phosphatase (ALP), creatine kinase (CK), glucose (GLU), uric acid (UA), blood urea nitrogen (BUN)/urea (Urea), creatinine (Cr), sodium (Na), potassium (K), calcium (Ca), phosphorus (P), magnesium (Mg), and chloride (Cl). The first dose was administered within 7 days after the examination during the screening period, and if the dose was not administered after 7 days of the examination and the investigator assessed that re-judgment was required, an additional examination could be performed, starting from Cycle 2, before dosing on Day 1 of each cycle, and on Day 8.

g. Hematology includes: white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), platelet (PLT), hematocrit (HCT), neutrophil (NEU), eosinophil (EOS), basophil (BAS), monocyte (MON), lymphocyte (LYM), etc.; hematology in Cycle 1 is scheduled on Day 1 (within 24 hours before administration), Day 3, Day 8, Day 10, Day 15, and baseline hematology should be performed within 24 hours before the first study dose; hematology in other cycles is performed on Days 1 and 8 of each cycle, and the examination on Day 1 of each cycle is performed before administration. Subjects were eligible for chemotherapy administration as determined by predose hematology results on Day 1 of each cycle.

	Screening Period	Treatment Period [a] (21 days per cycle, 6 cycles)										Safety Visit [b]	Survival Follow-up [c]
		Cycle 1						Cycle 2 and above					
	D-21 ~ -1	D1	D2	D3	D8	D10	D15	D1	D2	D3	D8	+ 30 days	Every 60 days
Window (Days)					± 1	± 1	± 1	± 3			± 1	± 7	± 7

h. Urine examination includes: urine protein, urine pH, urine ketone body, urine glucose, urine red blood cells, urine white blood cells and so on. The first dose was administered within 7 days after the examination during the screening period, and if the dose was not administered after 7 days of the examination and the investigator assessed that re-judgment was required, an additional examination could be performed, starting from Cycle 2, before dosing on Day 1 of each cycle, and on Day 8.

i. Women of childbearing potential only.

j. Baseline imaging was performed within 21 days prior to the first dose, every 6 ± 1 weeks after the first dose, or more frequently if clinically indicated. Imaging time should follow calendar days and should not be adjusted for treatment delays or terminations, and subjects who discontinue study drug for unacceptable toxicity or other reasons other than disease progression should continue to be followed for tumor assessments until disease progression, receipt of new antineoplastic therapy, withdrawal from study, or death, whichever occurs first

k. For Cycle 1 only, blood sampling time points are detailed in Chapter 6 Pharmacokinetics.

l. Chemotherapy: carboplatin - administered on Day 1 of each 21-day cycle with target AUC (Calvert formula) = 5 (maximum dose 750 mg) by intravenous infusion over 30 min; etoposide - administered on Days 1, 2, and 3 of each 21-day cycle with 100 mg/m^2 by intravenous infusion over 60 min; trilacicilb/placebo: administered every 21 days as 240 mg/m^2 before chemotherapy on Days 1, 2, and 3 of each 21-day cycle with 5% glucose injection or normal saline prepared into 250 mL solution by intravenous infusion over 30 min (as far as PK studies are involved). Subjects in Part I will receive Trilaciclib plus EC regimen and subjects in Part II may receive Trilaciclib or placebo plus EC regimen. Date of medication visit is based on the first dose of investigational drug (Trilaciclib/Placebo) in each cycle (D1).

m. Hepatitis B and C screening were performed during the screening period, five items of hepatitis B: if hepatitis B surface antigen (HBsAg) was positive or hepatitis B core antibody (HBcAb), HBV-DNA should be added; hepatitis C examination: if hepatitis C antibody was positive, HCV-RNA should be added.

2/3 Line ES-SCLC Patient Study Flow (Topotecan)

	Screening Period	Treatment Period [a] (21 days per cycle until disease progression or intolerable)													Safety Visit [b]	Survival Follow-up [c]
		Cycle 1								Cycle 2 and above						
	D-21 ~ -1	D1	D2	D3	D4	D5	D10	D12	D15	D1	D2	D3	D4	D5	D10	+ 30 days	Every 60 days
Window (Days)							± 1	± 1	± 1	± 3					± 1	± 7	± 7
Informed Consent	X																
Demographic information	X																
Past medical history [d]	X																
Checked in/out	X																
Randomization (Part II only)	X																
ECOG	X	X								X						X	
Physical examination	X						X			X						X	
Body height [e]	X	X								X							
Vital signs	X						X			X						X	
Biochemistry	X								X	X					X	X	

	Screening Period	Treatment Period [a] (21 days per cycle until disease progression or intolerable)														Safety Visit [b]	Survival Follow-up [c]
		Cycle 1								Cycle 2 and above							
	D-21 ~ -1	D1	D2	D3	D4	D5	D10	D12	D15	D1	D2	D3	D4	D5	D10	+ 30 days	Every 60 days
Window (Days)							± 1	± 1	± 1	± 3					± 1	± 7	± 7
[f]																	
Hematology [g]	X	X				X [g]	X	X [g]	X [g]	X					X	X	
Urine test [h]	X									X					X	X	
12-lead ECG	X									X						X	
Serum Pregnancy [i]	X																
Tumor assessment [j]	X	Imaging every 6 ± 1 week after first study drug dose															
PK (Part I) [k]		Day 1-6 blood sampling															
PK (Part II) [k]		Day 1-2 blood sampling															
Trilaciclib/Placebo [l]		X	X	X	X	X				X	X	X	X	X			
Topotecan [l]		X	X	X	X	X				X	X	X	X	X			
Virology [m]	X																
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival and other anti-tumor																	X

	Screening Period	Treatment Period [a] (21 days per cycle until disease progression or intolerable)														Safety Visit [b]	Survival Follow-up [c]
		Cycle 1								Cycle 2 and above							
	D-21 ~ -1	D1	D2	D3	D4	D5	D10	D12	D15	D1	D2	D3	D4	D5	D10	+ 30 days	Every 60 days
Window (Days)							± 1	± 1	± 1	± 3					± 1	± 7	± 7
conditions																	

a. Trilaciclib + Topotecan chemotherapy will be administered in 21-day cycles until disease progression, intolerability, or treatment discontinuation at the investigator 's discretion.
b. Follow-up was performed 30 days (± 7 days) after the last dose, at the start of a new anticancer therapy (-7 days), or at study withdrawal (-7 days), whichever came first.
c. Survival follow-up refers to telephone follow-up once at 60 days (± 7 days) after the last dose to collect other anti-tumor information until 50% of subjects die.
d. Smoking history, family history and relevant medical history of tumor diagnosis and treatment should be collected for medical history; symptoms, signs, laboratory abnormalities within 4 weeks before signing the informed consent form, medication history within 14 days before signing the informed consent form, and weight change within 6 months (> or < 5%). Results of examinations performed at our hospital within 21 days prior to the first dose (Part I) or randomization (Part II) and meeting the requirements of this protocol prior to signing of informed consent (hematology, biochemistry, and urine tests need to be performed within 7 days prior to the first dose of each trial part, pregnancy tests need to be performed within 21 days prior to the first dose of each trial part, and viral and pregnancy tests can be performed outside hospital) can be used for screening assessments without the need for the same tests during the screening period. Patients who fail the initial screening may not be rescreened (only once) until consultation with the Sponsor 's designated medical representative and approval by the Sponsor.
e. Height will be measured only at Screening and weight will be measured pre-dose every cycle except Screening.
f. Biochemistry tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GT), lactate dehydrogenase (LDH), cholesterol (TC), triglyceride (TG), total bilirubin (TBIL), direct bilirubin (DBIL), total protein (TP), albumin (ALB), alkaline phosphatase (ALP), creatine kinase (CK), glucose (GLU), uric acid (UA), blood urea nitrogen (BUN)/urea (Urea), creatinine (Cr), sodium (Na), potassium (K), calcium (Ca), phosphorus (P), magnesium (Mg), and chloride (Cl). The first dose was administered within 7 days after the examination during the screening period, and if the dose was not administered after 7 days of the examination and the investigator assessed that re-judgment was required, an additional examination could be performed, starting from Cycle 2, before dosing on Day 1 of each cycle, and on Day 10.
g. Hematology includes: white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), platelet (PLT), hematocrit (HCT), neutrophil (NEU), eosinophil (EOS), basophil (BAS), monocyte (MON), lymphocyte (LYM), etc.; hematology in Cycle 1 is scheduled on Day 1 (within 24 hours before dosing), Day 5, Day 10, Day 12, Day 15, and baseline hematology should be performed within 24 hours before the first study dose; hematology in other cycles is performed on Days 1 and 10 of each cycle, and the examination on Day 1 of each cycle is performed before dosing. Subjects were eligible for chemotherapy administration as determined by predose hematology results on Day 1 of each cycle.
h. Urine examination includes urine protein, urine pH, urine ketone body, urine glucose, urine red blood cells, urine white blood cells, etc. The first dose is administered within 7 days after the examination during the screening period. If the dose is not administered after 7 days of the examination and the investigator considers it necessary to make a re-judgment, an additional test may be performed from Cycle 2, before administration on Day 1 of each cycle, and on Day 10.
i. Women of childbearing potential only.
j. Baseline imaging was performed within 21 days prior to the first dose, every 6 ± 1 week after the first dose, or more frequently if clinically indicated. Imaging examinations should follow calendar days and should not be modified for treatment delays or terminations, and subjects who discontinue study drug for unacceptable toxicity or other reasons other than disease progression should continue to be followed for tumor assessments until disease progression, receipt of new antineoplastic therapy, withdrawal from the study, or death, whichever occurs first.
k. For Cycle 1 only, blood sampling time points are detailed in Chapter 6 Pharmacokinetics.
l. Chemotherapy: Topotecan will be administered at 1.25 mg/m^2 on Days 1-5 of each 21-day cycle via intravenous drip over 30 min; Trilacicilb/placebo: will be administered at 240 mg/m^2 on Days 1-5 of each 21-day cycle via intravenous drip over 30 min using 5% glucose injection or normal saline as 250 mL solution before chemotherapy due to PK study. The first of these

	Screening Period	Treatment Period [a] (21 days per cycle until disease progression or intolerable)													Safety Visit [b]	Survival Follow-up [c]
		Cycle 1								Cycle 2 and above						
	D-21 ~ -1	D1	D2	D3	D4	D5	D10	D12	D15	D1	D2	D3	D4	D5	D10	+ 30 days	Every 60 days
Window (Days)							± 1	± 1	± 1	± 3					± 1	± 7	± 7

subjects will receive Trilaciclib plus Topotecan and the second will likely receive Trilaciclib or placebo plus Topotecan. Date of medication visit is based on the first dose of investigational drug (Trilaciclib/Placebo) in each cycle (D1).

m. Hepatitis B and C screening were performed during the screening period, five items of hepatitis B: if hepatitis B surface antigen was positive or hepatitis B core antibody was positive (HBcAb), HBV-DNA should be added; hepatitis C examination: if hepatitis C antibody was positive, HCV-RNA should be added.

5.3. Appendix 3 Criteria for CTCAE judgment of laboratory parameters

Laboratory parameters will be graded primarily using CTCAE version 5.0. CTCAE grading of some indicators cannot be based on CTCAE Version 5.0, requires clinical diagnosis or clinical diagnosis and value determination, and cannot be completely divided by programming, such as hyperglycemia, hypokalemia, hypophosphatemia, hyponatremia and hyperuricemia, which will be graded using CTCAE Version 4.03.

Parameter	Level				
	1	2	3	4	5
Albumin	< lower limit of normal – 3 g/dL; < lower limit of normal – 30 g/L	< 3 – 2 g/dL; < 30 – 20 g/L	< 2 g/dL; < 20 g/L	Life-threatening; urgent intervention indicated	Death
ALP Alkaline phosphatase	> upper limit of normal - 2.5 times upper limit of normal (normal baseline); 2 to 2.5 times baseline (abnormal baseline)	> 2.5 to 5.0 times the upper limit of normal (normal baseline); > 2.5 to 5.0 times the baseline (if abnormal baseline)	> 5.0 to 20.0 times upper limit of normal (normal baseline); > 5.0 to 20.0 times baseline (if abnormal baseline)	> 20.0 times upper limit of normal (normal baseline); > 20.0 times baseline if baseline is abnormal	-
ALT Alanine Aminotransferase	> upper limit of normal - 3 times upper limit of normal (normal baseline); 1.5 to 3.0 times baseline (if abnormal baseline)	3 to 5 times the upper limit of normal (normal baseline), > 3.0 to 5.0 times baseline (if baseline is abnormal)	5 to 20-fold (if baseline is normal); > 5 to 20-fold (if baseline is abnormal)	> 20 x upper limit of normal (if baseline is normal); > 20 x baseline (if baseline is abnormal)	-
AST Aspartate Aminotransferase	> upper limit of normal - 3 times normal Upper limit (normal baseline); baseline	> 3-5 times upper limit of normal (normal baseline);	> 5.0 - 20.0 of upper limit of normal Fold (normal baseline); > baseline	> 20.0 times upper limit of normal (normal baseline);	-

Transaminase	1.5 to 3.0 times (if baseline value is abnormal)	> 3.0 - 5.0 of baseline Fold (Abnormal Baseline)	5.0-20.0 fold (if baseline is abnormal)	> 20.0 times baseline if baseline is abnormal	
Hypercholesterolemia	> upper limit of normal ~ 300 mg/dL or > upper limit of normal ~ 7.75 mmol/L	> 300 - 400 mg/dL 7.75 Or > - 10.34 mmol/L	> 400 - 500 g/dL 10.34 - Or > 12.92 mmol/L	> 500 mg/dL or > 12.92 mmol/L	-
Hypertriglyceridemia	150 mg/dL to 300 mg/dL or 1.71 mmol/L to 3.42 mmol/L	> 300 mg/dL to 500 mg/dL or > 3.42 mmol/L to 5.7 mmol/L	> 500 mg/dL to 1000 mg/dL or > 5.7 mmol/L to 11.4 mmol/L	Life Threatening	Death
Blood bilirubin increased	> upper limit of normal ~ 1.5 times upper limit of normal (normal baseline); > 1 ~ 1.5 times baseline (abnormal baseline)	Greater than 1.5 to 3.0 times the upper limit of normal (normal baseline); greater than 1.5 to 3.0 times the baseline (abnormal baseline)	Greater than 3.0 to 10 times the upper limit of normal (normal baseline); greater than 3.0 to 10 times the baseline (abnormal baseline)	Greater than 10 times upper limit of normal (normal baseline); greater than 10 times baseline (abnormal baseline)	-
Creatinine increased	> upper limit of normal ~ 1.5 times upper limit of normal	> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x normal Limit	> 3.0 times baseline value; > 3.0 ～ 6.0 x upper limit of normal	> 6.0 x upper limit of normal	-
Creatinine clearance rate (CrCl)	Creatinine clearance (CrCl) less than 60 mL/min/1.73 m2	CrCl 59 ~ 30 mL/min/1.73 m2	CrCl 29 ~ 15 mL/min/1.73 m2	CrCl Small in 15 mL/min/1.73 m2; requiring dialysis or renal transplant	Death

Hypercalcaemia (Corrected for albumin)	Corrected serum calcium > upper limit of normal ~ 11.5 mg/dL; > upper limit of normal Limit: ~ 2.9 mmol/L; Ionized calcium concentration > upper limit of normal ~ 1.5 mmol/L	Corrected serum calcium > 11.5 - 12.5 mg/dL; > 2.9 - 3.1 mmol/L; calcium concentration > 1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium > 12.5 - 13.5 mg/dL; > 3.1 - 3.4 mmol/L; calcium concentration > 1.6 - 1.8 mmol/L; hospitalization required	Corrected serum calcium > 13.5 mg/dL; > 3.4 mmol/L; ionized calcium concentration > 1.8 mmol/L; life-threatening	Death
Hypocalcemia (Corrected for albumin)	Corrected serum calcium < lower limit of normal ~ 8.0 mg/dL; < lower limit of normal ~ 2.0 mmol/L; calcium concentration < lower limit of normal ~ 1.0 mmol/L	Corrected serum calcium < 8.0 - 7.0 mg/dL; < 2.0 - 1.75 mmol/L; calcium concentration < 1.0 ~ 0.9 mmol/L; symptomatic	Corrected serum calcium < 7.0 - 6.0 mg/dL; < 1.75 - 1.5 mmol/L; calcium concentration < 0.9 ~ 0.8 mmol/L; hospitalization required	Corrected serum calcium < 6.0 mg/dL; < 1.5 mmol/L; ionized calcium concentration < 0.8 mmol/L; life-threatening	Death
CK creatine phosphokinase	> upper limit of normal ~ 2.5 times upper limit of normal	> 2.5 x upper limit of normal to 5 x upper limit of normal	> 5 x upper limit of normal to 10 x upper limit of normal	> 10 x upper limit of normal	-
Gamma glutamyl transferase (GGT)	> 1 to 2.5 times the upper limit of normal if baseline is normal or 2.0 to 2.5 times the baseline level if baseline is abnormal	> 2.5 ～ if baseline value is normal 5.0 x upper limit of normal; > 2.5 to 5.0 x baseline if baseline is abnormal	> 5.0 ～ if baseline value is normal 20. times the upper limit of normal; if the baseline value is abnormal, > 5.0 ~ 20.0 times the baseline level	> 20.0 x upper limit of normal if baseline is normal or > 20.0 x baseline if baseline is abnormal	-

Hyperglycemia (CTCAE 4.03)	Fasting blood glucose greater than upper limit of normal - 160 mg/dL or Fasting blood glucose greater than upper limit of normal - 8.9 mol/L	Empty abdominal blood glucose greater than 160-250 mg/dL or fasting plasma glucose greater than 8.9-13.9 mol/L	Empty abdominal blood sugar greater than 250-500 mg/dL or fasting plasma glucose greater than 13.9-27.8 mol/L	Fasting glucose greater than 500 mg/dL or 27.8 mol/L	-
Hypoglycemia	< lower limit of normal ~ 55 mg/dL; < lower limit of normal ~ 3.0 mmol/L	< 55 - 40 mg/dL; < 3.0 - 2.2 mmol/L	< 40-30 mg/dL; < 2.2-1.7 mmol/L	< 30 mg/dL; < 1.7 mmol/L; life-threatening; seizure	Death
Hemoglobin	Hemoglobin < lower limit of normal ~ 10.0 g/dL; < lower limit of normal ~ 6.2 mmol/L; < lower limit of normal ~ 100 g/L	Hemoglobin < 10.0 - 8.0 g/dL; < 6.2 - 4.9 mmol/L; < 100 - 80 g/L	Hemoglobin < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening; urgent treatment required	Death
Lipase increased	> 1.5 x upper limit of normal (ULN) ULN	> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN and asymptomatic	> 2.0 - 5.0 times ULN with signs or symptoms; > 5.0 times ULN but no symptoms	> 5.0 x ULN with signs or symptoms	-
Hyperkalemia	> upper limit of normal ~ 5.5 mmol/L	> 5.5 - 6.0 mmol/L; intervention	> 6.0 - 7.0 mmol/L; hospitalization required	> 7.0 mmol/L; life-threatening	Death
Hypokalemia (CTCAE 4.03)	< lower limit of normal (LLN) to 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L	-

Lymphocyte count	< lower limit of normal ~ 800/mm ^{3} ; < lower limit of normal ~ 0.8 x 10 ^{9}/L	< 800 - 500/mm ^{3} ; < 0.8 - 0.5 x 10 ^{9}/L	< 500 - 200/mm ^{3} ; < 0.5 - 0.2 x 10 ^{9}/L	< 200/mm ^{3} ; < 0.2 x 10 ^{9}/L	-
Neutrophil count	< lower limit of normal ~ 1500/mm ^{3} ; < lower limit of normal ~ 1.5 x 10 ^{9}/L	< 1500 - 1000/mm ^{3} ; < 1.5 - 1.0 x 10 ^{9}/L	< 1000 - 500/mm ^{3} ; < 1.0 - 0.5 x 10 ^{9}/L	< 500/mm ^{3} ; < 0.5 x 10 ^{9}/L	-
Hypophosphatemia (CTCAE 4.03)	< lower limit of normal ~ 2.5 mg/dL or < lower limit of normal ~ 0.8 mmol/L	< 2.5 - 2.0 mg/dL or < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL or < 0.6 - 0.3 mmol/L	< 1.0 mg/dL or < 0.3 mmol/L	-
Hypomagnesemia	< lower limit of normal ~ 1.2 mg/dL; < lower limit of normal ~ 0.5 mmol/L	< 1.2 - 0.9 mg/dL; < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL; < 0.4 - 0.3 mmol/L	< 0.9 - 0.7 mg/dL; < 0.4 - 0.3 mmol/L	Death
Hypermagnesaemia	> upper limit of normal ~ 3.0 mg/dL; > upper limit of normal ~ 1.23 mmol/L	-	> 3.0 - 8.0 mg/dL; > 1.23 to 3.30 mmol/L	> 8.0 mg/dL; > 3.30 mmol/L; Life Threatening	Death
Platelet count	< lower limit of normal ~ 75,000/mm ^{3} ; < lower limit of normal ~ 75.0 x 10 ^{9}/L	< 75,000 to 50,000/mm ^{3} ; < 75.0 - 50.0 x 10 ^{9}/L	< 50,000 to 25,000/mm ^{3} ; < 50.0 - 25.0 x 10 ^{9}/L	< 25,000/mm ^{3} ; < 25.0 x 10 ^{9}/L	-

Hypernatremia	> upper limit of normal ~ 150 mmol/L	> 150 - 155 mmol/L; intervention	> 155 - 160 mmol/L; hospitalization required	> 160 mmol/L; life-threatening	Death
Hyponatremia (CTCAE 4.03)	< lower limit of normal ~ 130 mmol/L	-	130 to 120 mmol/L with or without symptoms	< 120 mmol/L	-
Leucocyte	< lower limit of normal ~ 3000/mm^3 ; < lower limit of normal ~ 3.0 x 10^9/L	< 3000 - 2000/mm^3 ; < 3.0 - 2.0 x 10^9/L	< 2000 - 1000/mm^3 ; < 2.0 - 1.0 x 10^9/L	< 1000/mm^3 ; < 1.0 x 10^9/L	-

5.4. Appendix 4 Window Visits

During the treatment cycle, if more than one visit occurred within a window visit, the visit closest to the scheduled date was selected; if the distance between two visits and the scheduled date was the same, the visit occurring later was selected as the window visit; and if multiple visits occurred on the same day, the worst case was selected.

Visit Window - 1L Subject

	Cycle 1						Cycle 2 and above			Safety Visit
Visits	D1	D3	D8	D10	D15	End	D1	D8	End	
Scheduled Date[a]	1	3	8	10	15	22	1	8	22	30 (+ 3)
Biochemistry	-3 to 1		2 to 11		12 to 18	19 to end of cycle	-3 to 1	2 to 15	16 to end of cycle	Date of first dose of last cycle to 40 days after first dose
Hematology	-1 to 1	2 to 5	6 to 9	10 to 12	13 to 18	19 to end of cycle	-3 to 1	2 to 15	16 to end of cycle	Date of first dose of last cycle to 40 days after first dose

[a] Relative to Day 1 of each cycle

Visit Window - 2/3L Subject

	Cycle 1						Cycle 2 and above			Safety Visit
Visits	D1	D5	D10	D12	D15	End	D1	D10	End	
Scheduled Date [a]	1	5	10	12	15	22	1	10	22	30 (+ 5)
Biochemistry	-3 to 1				2 to 18	19 to end of cycle	-3 to 1	2 to 16	17 to end of cycle	Date of first dose of last cycle to after first dose 42 days
Hematology	-1 to 1	2 to 7	8 to 11	12 to 13	14 to 18	19 to end of cycle	-3 to 1	2 to 16	17 to end of cycle	Date of first dose of last cycle to after first dose 42 days

[a] Relative to Day 1 of each cycle