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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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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Sponsor:	Jiangsu Simcere Pharmaceutical Co., Ltd.

VERSION HISTORY/REVISION HISTORY

Version No.	Version Date	Reason for Amendment Description and Summary of Changes
1.0	20201019	First draft
1.1	20210113	Mainly modified study endpoints and increased exploration of population pharmacokinetic profiles
1.2	20210119	Mainly modified some language expressions to be succinct and clear; added pharmacokinetic blood sampling points
1.3	20210817	Add two other study secondary endpoints, chemotherapy drug dose adjustment recommendations, adjust timepoint and unblinding form of the main analysis of Part II, definition of the end of the study, adjust other sections and errata
1 .4	20220321	Clarification of safety visit timepoints, full text errata, etc.

Note: See also Annex Revision Summary for detailed revisions

Sponsor Protocol Signature Page

We have read and confirmed this clinical trial protocol. I agree to perform my duties in accordance with the laws of China, the Declaration of Helsinki, China 's GCP, and this study protocol.

Sponsor: Jiangsu Simcere Pharmaceutical Co., Ltd

Address of Sponsor: [redacted]

Authorized signature by sponsor: [redacted] **Title:** [redacted]

Tel.: [redacted]

Address: [redacted]

Signature: Date:

Principal Investigator Protocol Signature Page

I have read this protocol and agree that it contains all necessary details to conduct the study.

I will conduct this clinical study in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and applicable regulatory regulations.

This trial protocol can only be implemented after being reviewed and approved by the Ethics Committee and signed with approval comments. This protocol and related information are confidential and should not be disclosed to other persons unrelated to this trial or used for any purpose other than this study without the written permission of the sponsor.

Signature confirms approval of the clinical protocol.

Study Site:

Investigator Name:

Tel.:

Signature: Date:

Contents

List of Tables

Abbreviation

Abbreviation	Full Name
AE	Adverse Event
ANC	Absolute Neutrophil Count
AUC	Area under concentration-time curve
CDK4/6	Cyclin-dependent kinases 4 and 6
CIA	Chemotherapy induced anemia
CIM	Chemotherapy induced myelosuppression
CIN	Neutropenia
CIT	Chemotherapy induced thrombocytopenia
C_{max}	Maximum plasma concentration
Cyc	Cyclin
CYPs	Cytochromases
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleotide
DSN	Duration of severe neutropenia
ECOG	Eastern Cooperative Oncology Group
ESA	Erythropoiesis Stimulating Agent
ES-SCLC	Extensive stage small cell lung cancer
FDA	Food and Drug Administration
FAS	Full Analysis Set
FN	Febrile neutropenia
FOB	Functional Observation Battery
G-CSF	Granulocyte colony-stimulating factor
HRQoL	Health-related quality of life
HSC	Hematopoietic stem cell
HSPC	Hematopoietic stem and progenitor cell
IEC	Independent Ethics Committee
ICI	Immune checkpoint inhibitors
IWRS	Interactive web response system
Kd	Dissociation constant
K_i	Inhibition constant
MATE	Multidrug and toxin extrusion
Min	Minute
MOA	Mechanism of action
NOEL	No observed effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PDUFA	Prescription Drug User Fee Act
PFS	Progression-free survival
PK	Pharmacokinetics
PRO	Patient Reported Outcomes
Rb	Retinoblastoma

Abbreviation	Full Name
RBC	Red blood cell
RES	Response Assessment Analysis Set
SAE	Serious Adverse Event
SCLC	Small cell lung cancer
SS	Safety Analysis Set
TEAE	Treatment-emergent adverse event
TNBC	Triple negative breast cancer
PK/PD	Pharmacokinetics/Pharmacodynamics

Protocol Synopsis

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	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

RATIONALE	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 was defined as death in 75% of subjects, or 12 months after the last subject was 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 was 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 was 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) was 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:** <u>Cycle 1 Day 1:</u> 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 was performed according to RECIST1.1. 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. 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 was 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 was 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 was 10% in the Trilaciclib group and 45% in the placebo group, the means of Poisson distributions were 0.105 and 0.598 for the corresponding Trilaciclib and placebo groups, respectively. The stochastic simulation was 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 was 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 was 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 was 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 was $< 0.5 \times 10^9$/L, and (2) there were 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 was counted as Day 1 of Cycle 2). If the subject did not experience any SN during Cycle 1, DSN in Cycle 1 was 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 were also 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.

1. Study Background

Trilaciclib (Cosela™) is a highly selective, reversible CDK4/6 small molecule inhibitor with novel chemical structures that transiently stays hematopoietic stem and progenitor cells (HSPCs) in the G0/G1 phase in bone marrow. Therefore, for CDK4/6-independent tumors (such as small cell lung cancer [SCLC], etc.), Trilaciclib combined with chemotherapy can protect the bone marrow without antagonizing the anti-tumor efficacy of chemotherapy.

Trilaciclib received Breakthrough Therapy Designation from the US Food and Drug Administration (FDA) in August 2019 based on its robust and significant myeloprotective efficacy demonstrated in 3 clinical trials in SCLC. The sponsor's U.S. partner, G1 Therapeutics, has received U.S. FDA marketing approval in February 2021, based on the results of these three studies in SCLC, for the use of Trilaciclib in patients with small cell lung cancer treated with a platinum-containing combination etoposide regimen or a topotecan-containing regimen to reduce the occurrence of chemotherapy-induced myelosuppression.

The efficacy and safety of Trilaciclib have been confirmed based on three randomized controlled clinical trials conducted in SCLC that have been completed overseas. There is no evidence that the response to drug treatment in Chinese patients differs from that in overseas populations.

At present, there is no relevant data on the use of Trilaciclib in the Chinese population in clinical trials of Trilaciclib, so the safety and efficacy of Trilaciclib in Chinese patients need to be further evaluated. A single-arm, open-label safety and PK study and a randomized double-blind, placebo-controlled study are planned to be conducted in extensive stage small cell lung cancer in China in phase I/III clinical trials.

1.1. Background and rationale

1.1.1. Chemotherapy induced myelosuppression (CIM) is a serious and life-threatening disease

Chemotherapy-induced myelosuppression (CIM) is a common and important side effect during cancer treatment, mainly manifested as neutropenia, anemia and thrombocytopenia. Patients with myelosuppression are more likely to experience infections, sepsis, bleeding, and reductions in health-related quality of life (HRQoL), frequent hospitalizations, and even death [1-4]. In addition, CIM often results in drug dose reduction or delay, and limitations in the dose intensity of chemotherapeutic agents may reduce the antitumor efficacy of chemotherapy.

Chemotherapy induced neutropenia (CIN) is a severe manifestation of CIM, the consequences of which depend on the severity and duration of the neutropenia event. In a

retrospective analysis of patients with small cell lung cancer (SCLC), non-Hodgkin lymphoma, head and neck cancer, or breast cancer, 77.5% were at high risk for febrile neutropenia (FN) during chemotherapy, while 18.8% were hospitalized for infection during the first course. For patients with Grade 3 or 4 CIN, each additional day of duration was associated with a 28% (95% confidence interval [CI]: 7%, 51%) or 30% (95% CI: 10%, 54%) increased risk of infection-related hospitalization [4]. The results of a study showed that for patients with neutropenia requiring hospitalization, in-hospital mortality was estimated to be between 3.4% and 10.5% for patients with different tumor types, and the overall mortality was 6.8% [1]. In another analysis, the overall in-hospital mortality was 9.5%, with solid tumor mortality ranging from 3.6% for breast cancer to 13.4% for lung cancer [5].

Chemotherapy induced anemia is another serious clinical manifestation of CIM that impacts HRQoL, increases the incidence of associated adverse events, and leads to increased mortality. Moderate-to-severe anemia is associated with fatigue and dyspnea in patients with multiple cancer types. However, SCLC patients tend to be very elderly smokers and have cardiopulmonary comorbidities, making anemia a more clinically significant consequence. For patients diagnosed with chronic heart failure, hemoglobin levels ≤ 10 g/dL increase the risk of death approximately 2-fold [6]. Similarly, in a broader nononcology patient population, patients with chronic obstructive pulmonary disease (COPD) who presented with hemoglobin levels below 13 g/dL had shorter median overall survival (OS: 49 versus 74 months) compared with patients without a diagnosis of anemia [7].

The clinical prognosis of chemotherapy-induced thrombocytopenia (CIT) depends on the degree and duration of platelet count reduction. Chemotherapy regimens used to treat cancer patients with solid tumors have a relatively lower risk of serious long-term thrombocytopenia compared to patients with hematologic malignancies, and therefore the risk/consequences of bleeding associated with this have received less attention. However, thrombocytopenia can lead to some clinically relevant problems in specific patient subpopulations, such as patients with brain metastases or those requiring long-term anticoagulant therapy, or in patients requiring specific chemotherapy regimens, such as topotecan. At the same time, with the accumulation of chemotherapy courses, the severity of CIT will also be aggravated due to the continuous suppression of bone marrow by the accumulation of chemotherapy drug doses. Because there are limited treatments for CIT, once it occurs, the duration and impact on subsequent chemotherapy tend to be more severe than CIN.

1.1.2. Current therapies and unmet clinical needs for CIM

The only treatment for severe (Grade 4) neutropenia (SN) is growth factors, but not recommended for all patients receiving myelosuppressive chemotherapy. For patients with FN risk ≤ 20% [8-9] growth factors are not recommended until the patient experiences an adverse event. In addition, these drugs can cause serious side effects, such as bone pain, which in severe cases may be intolerable to the patient. For example, in a retrospective pooled analysis, approximately 30% of patients treated with pegfilgrastim experienced grade ≥ 2 bone pain [10]. There is no effective treatment for patients who cannot tolerate growth factors.

Chemotherapy induced anemia (CIA) is one of the important manifestations of chemotherapy induced myelosuppression. To date, the only treatment for CIA has been transfusion or transfusion of erythropoiesis stimulating agents (ESAs), neither of which is a perfect intervention. In addition to being a temporary solution to this serious situation, red cell transfusion carries the risk of latent infection, immunosuppression, alloimmunization, and transfusion reactions. ESAs also have serious side effects, including increased risk of myocardial infarction, cerebrovascular accident, and thromboembolism, decreased OS, and lead to tumor progression/recurrence.

Chemotherapy-induced thrombocytopenia (CIT) refers to one of the most common cancer treatment complications in which anti-tumor chemotherapeutic drugs exert an inhibitory mechanism on the bone marrow, especially on megakaryocytic cells, resulting in platelet counts in peripheral blood lower than normal values, and is a common hematological toxicity in clinical practice. Treatment of CIT includes platelet transfusions and administration of thrombopoietic growth factors, which are mainly recombinant human interleukin 11 and recombinant human thrombopoietin [11]. Platelet transfusion is one of the fastest and most effective treatments for patients with severe thrombocytopenia. However, platelet transfusion may potentially bring about the risk of infection with acquired infectious viral diseases such as AIDS and hepatitis C, as well as some complications related to platelet transfusion. Patients may also produce platelet antibodies and cause ineffective platelet transfusion or immune response after transfusion. Thrombus caused by platelet elevation has always been one of the potential risks of application of platelet-stimulating growth factor [12]. Close attention should be paid to platelet changes after administration and timely drug withdrawal is required, which also limits its application in clinical trials.

In addition, dose reduction and delay are common clinical measures to cope with CIM. These dose modifications limit the relative dose intensity (RDI) of the planned treatment, which

may reduce the potential benefit to patients [13-15] and also put pressure on patients, who are concerned about worsening their disease if they are not treated as prescribed.

Thus, despite some targeted clinical interventions for clinically significant CIM, cancer patients still suffer from symptoms associated with infection, anemia, and thrombocytopenia, transfusion requirements, delayed dosing, and dose reductions; as well as an increased risk of long-term complications of myelosuppression and growth factor use (in long-term survivors). The continued occurrence of risk events resulting from these CIMs suggests the need for additional interventions to improve the current standard of care (SOC).

Currently, there are no effective therapies that can prevent or mitigate chemotherapy-induced myelosuppression before chemotherapy occurs. Although growth factors (granulocyte colony-stimulating factors [G-CSFs] and erythropoiesis stimulating agent [ESAs]) and blood transfusions can be used to treat myelosuppression, these "reactive" interventions are specific to a cell lineage, used after chemotherapy has harmed them, and pose risks to patients that are inherent to their treatment itself. G-CSF is administered following chemotherapy treatment even in the setting of primary prevention (ie, administered during the first cycle of chemotherapy and not triggered by the development of adverse events [AEs]) to stimulate proliferation of surviving progenitor cells. Chemotherapy still caused irreversible damage to the bone marrow. An alternative approach that can replace "reactive" intervention therapies, thereby protecting bone marrow from the cytotoxicity of chemotherapy to simultaneously protect multiple lineages, is of great clinical benefit.

This need is particularly acute in patients treated for small cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancers, with approximately 70% of patients already in the extensive stage at initial diagnosis. Major diagnosis and treatment guidelines at home and abroad (including those edited by the Chinese Society of Clinical Oncology) recommend platinum-based chemotherapy as the first-line standard treatment for SCLC. Studies have shown that platinum-based combination therapy with etoposide or topotecan in the treatment of extensive stage small cell lung cancer is highly susceptible to significant myelosuppression (neutropenia 47% to 92%, leukopenia 8% to 66%, thrombocytopenia 10% to 46% and anemia 7% to 34%) [16-21]. Consistent with the literature findings, the occurrence of Grade 4 neutrophils was as high as 52.9%, the occurrence of Grade 3/4 thrombocytopenia was 36.1%, and the occurrence of Grade 3/4 anemia was 31.9% in the control groups (ie, those receiving placebo and chemotherapy) in the three small cell lung cancer trials of Triliciclib, which has great room for improvement.

1.1.3. Chemotherapy and improving myelosuppression in small cell lung cancer in China

The results of epidemiological statistical study of malignant tumors in China in 2015 showed that 787,000 new cases of lung cancer and 631,000 deaths occurred each year. Small cell lung cancer (SCLC), as a histological subtype of lung cancer, accounts for about 15 ~ 25% of lung cancer patients, and extensive stage small cell lung cancer (ES-SCLC) accounts for about 70% of clinical diagnoses. For ES-SCLC, in line with the major international guidelines for diagnosis and treatment, the first-line chemotherapy regimen recommended by the Chinese Society of Clinical Oncology is cisplatin/carboplatin combined with etoposide, and the second-line chemotherapy regimen is topotecan. Literature studies have shown (Table 1) that chemotherapy-induced myelosuppression (grade 3/4 neutropenia 15.6% to 93.8%, anemia 0% to 33.3%, and thrombocytopenia 0% to 33.3%) [22-39] remains an urgent major adverse reaction in Asian populations, including China, South Korea, and Japan, for patients with small cell lung cancer receiving carboplatin/cisplatin combined with etoposide effects or topotecan.

Table 1 Summary of Occurrence of Myelosuppression in Asian Patients with Extensive Stage Small Cell Lung Cancer Receiving Platinum Combined with Etoposide/Topotecan

Investigations	Study Category	Country	Treatment group	N	Occurrence of Grade 3 or Higher Myelosuppression		
					Neutropenia	Anemia	Thrombocytopenia
Shun lu et al, 2015 [29]	Random control	CHINA	Endostar (7.5 mg/m^2, D1-14) + carboplatin + etoposide (60 mg/m^2, D1-5)	69	55.1%	1.4%	18.8%
			Carboplatin (AUC = 5, D1) + etoposide (60 mg/m^2, D1-5)	69	39.1%	2.9%	18.8%
Zhang Shucai et al, 2007 [31]	Random control	CHINA	Carboplatin (300 mg/m^2, D1) + etoposide (100 mg, D1-5)	32	15.6%	12.5%	12.5%
Ma Jin'an et al, 2006 [32]	Retrospective analysis	CHINA	Cisplatin (80 mg/m^2 in 3 days) + etoposide (100 mg/m^2, D1-3)	29	34.5%	13.8%	17.2%
			Carboplatin (300 mg/m^2, or AUC = 6, D1) + etoposide (120 mg/m^2, D1-3)	12	50%	33.3%	33.3%
Ren Li et al 1999 [33]	Random control	CHINA	Carboplatin (200 mg/m^2, D1) + Cisplatin (20 mg/m^2, D1) + Etoposide (100 mg/m^2, D1-5)	32	71.9%	-	18.8%
			Carboplatin (300 mg/m^2 D1) + etoposide (100 mg/m^2 D1-5)	32	93.8%	-	21.9%
IMpower133 (Japanese subgroup) [27]	Random control	JAPAN	Atezolizumab (1200 mg, D1) + carboplatin (AUC = 5, D1) + etoposide (100 mg/m^2, D1-3)	20	70%	15%	20%
			Placebo + carboplatin (AUC = 5) + etoposide (100 mg/m^2, D1-3)	20	68.3%	9.1%	18.2%

Investigations	Study Category	Country	Treatment group	N	Occurrence of Grade 3 or Higher Myelosuppression		
					Neutropenia	Anemia	Thrombocytopenia
Sun Yan et al., 2016	Random control	CHINA	Cisplatin (80 mg/m^2, D1) + etoposide (100 mg/m^2, D1-3)	150	44.0%	6.7%	7.3%
Cheng Ying et al 2019 [25]	Random control	CHINA	Cisplatin (80 mg/m^2, D1) + etoposide (100 mg/m^2, D1-3)	111	73.9%	15.3%	10.8%
Shi Yuankai et al., 2015 [30]	Random control	CHINA	Cisplatin (75 mg/m^2, D1) + etoposide (100 mg/m^2, D1-3)	32	71.9%	31.3%	18.8%
Xiaoqing.L, et al; 2013	Random control	CHINA	Cisplatin (75 mg/m^2) + etoposide (100 mg/m^2, D1-3)	31	41.9%	6.5%	3.2%
Yu Haifeng et al. 2010 [28]	Retrospective analysis	CHINA	Cisplatin (25 mg/m^2, D1-3) + etoposide (100 mg/m^2, D1-3)	19	31.6%	15.8%	0
Dae Seog Heo, et al.; 2018	Random control	Korea	Cisplatin (70 mg/m^2, D1) + etoposide (100 mg/m^2, D1-3)	189	71.7%	17.5%	13.2%
In-Jae Oh, et al. 2009	Random control	Korea	Cisplatin (60 mg/m^2) + etoposide (100 mg/m^2, D1-3)	76	67.5%	13.0%	16.9%
Zhang Liang et al 2019 [34]	Retrospective analysis	CHINA	Topotecan, 1.5 mg/m^2, D1-5	42	66.7%	23.8%	26.5%

Investigations	Study Category	Country	Treatment group	N	Occurrence of Grade 3 or Higher Myelosuppression		
					Neutropenia	Anemia	Thrombocytopenia
Li Zhihua et al, 2015 [35]	Retrospective analysis	CHINA	Topotecan, 0.75 – 1.2 mg/m^2, D1-5	29	31.00%	17.20%	10.30%
Li Li et al, 2001 [36]	Prospective single arm	CHINA	Topotecan, 1.2 mg/m^2, D1-5	40	30.00%	0.00%	7.50%
Zhu Zhou et al 2013 [37]	Retrospective analysis	CHINA	Topotecan, 1.5 mg/m^2, D1-5	22	40.90%	-	-
Zhao Mingli et al. 2011 [38]	Retrospective analysis	CHINA	Topotecan, 1.25-1.5 mg/m^2, D1-5	21	42.90%	14.30%	0
Inoue A et al, 2015 [39]	Random control	JAPAN	Topotecan, 1.0 mg/m^2, D1-5	30	87%	30%	40%

1.1.4. Trilaciclib, a novel prophylactic bone marrow protective agent

Trilaciclib is a highly potent, selective, and reversible CDK4/6 inhibitor that protects bone marrow by protecting hematopoietic stem cells and progenitor cells (HSPCs) when performing systemic chemotherapy. The proliferation and differentiation of HSPCs are highly dependent on CDK4/6 activity and are arrested in G1 phase of the cell cycle when exposed to appropriate doses of trilaciclib, so intravenous administration of trilaciclib before chemotherapy can save blood cells from damage by cytotoxic chemotherapeutic drugs of the cell cycle. Therefore, for CDK4/6-independent tumors, Trilaciclib combined with chemotherapy can protect the bone marrow without antagonizing the anti-tumor efficacy of chemotherapy.

For SCLC, RB protein, which is a downstream target protein of CDK4/6, has been shown to be almost absent in SCLC [37-41]. Detailed description of the genomic profile of SCLC using next generation sequencing methods has recently been reported in 2 articles, confirming the common occurrence of inactivation of driver mutations TP53 and RB-1 in SCLC [42-43]. Consistent with these findings, preclinical in vitro and in vivo studies have shown that exposure to Trilaciclib prior to chemotherapy does not attenuate the killing effect of of chemotherapy on RB-1 inactive tumors, including SCLC. Therefore, SCLC can be considered CDK4/6-independent due to near universal RB-1 inactivation, which means that adult SCLC patients treated with platinum-based/etoposide regimen can be treated with trilaciclib to prevent CIM.

Three randomized, double-blind Phase 2 clinical trials in SCLC patients demonstrated that Trilaciclib administered in combination with chemotherapy (including 1st and 2nd/3rd lines of chemotherapy) prevented or mitigated chemotherapy-induced myelosuppression. Integrated analysis of data from the three studies showed that Trilaciclib administered prior to chemotherapy reduced the duration of severe neutropenia in Cycle 1 from 4 days to 0 days, reduced the occurrence of severe neutropenia by 76% (53.3% to 12.8%, $p < 0.0001$), reduced the occurrence of Grade 3/4 anemia from 31.9% to 20.3% ($p = 0.0279$), and reduced the occurrence of Grade 3/4 thrombocytopenia from 36.1% to 19.5% ($p = 0.0067$). Based on these data, Trilaciclib received Breakthrough Therapy designation in the US in August 2019 and a marketing application has been submitted to the US FDA in June 2020 for the indication of the use of Trilaciclib in patients with small cell lung cancer receiving platinum-based plus etoposide or topotecan-based regimens for the prevention of chemotherapy-induced myelosuppression.

1.2. Preclinical data

This section provides a brief summary of the preclinical studies of Trilaciclib, which are detailed in the Investigator 's Brochure.

1.2.1. Pharmacology

In vitro, Trilaciclib (also known as G1T28) demonstrated potent inhibitory activity against human CDK4 and CDK6 with half maximal inhibitory concentration (IC_{50}) values of 1 and 4 nM, respectively, and was highly selective for CDK4 (> 1000-fold selectivity) over CDK2. Trilaciclib demonstrated reversible inhibition of CDK4/cyclin D1 with an inhibition constant (K_i) of 0.78 nM.

G1 arrest induced by G1T28 in HSPC was transient and readily reversible in both in vitro and in vivo models. In vivo analysis suggests that G1T28 administered in combination with myelosuppressive chemotherapy promotes recovery of complete blood count (CBC) and improves survival. In addition, animal models have shown that the effect of Trilaciclib in preventing myelosuppression persists after 4 cycles of Trilaciclib in combination with 5-fluorouracil (5-FU), which has a high degree of myelosuppression. Whereas the extent and duration of CBC nadir continued to worsen following each cycle of 5-FU alone, this was improved by the combination of G1T28 and 5-FU, and after Cycle 4, animals receiving G1T28 + 5- FU showed a faster CBC recovery rate compared to 5-FU alone. In line with this, G1T28 showed resistance to 5-FU induced DNA damage in HSPC compared to 5-FU alone in a single-dose study in all cycles of combination therapy, and this effect persisted. In addition, a bone marrow transplantation experiment in mice irradiated with lethal doses showed that bone marrow obtained from mice receiving 4 cycles of 5-FU combined with G1T28 was more potent in hematopoietic reconstitution after bone marrow transplantation compared with bone marrow obtained from mice receiving 4 cycles of 5-FU alone, suggesting that G1T28 combined with chemotherapy can protect stem cells compared with 5-FU alone.

In vitro analysis suggests that RB-1 inactivated cells are resistant to CDK4/6 inhibition and therefore co-treatment with G1T28 does not protect them from chemotherapy damage. Trilaciclib decreased Rb phosphorylation and induced potent G1 cell cycle arrest in a cell model with intact and functional retinoblastoma (Rb) protein signaling (CDK 4/6 dependent). This effect was transient and reversible, as cells returned to baseline levels and re-entered the cell cycle after Trilaciclib washout. In contrast, Trilaciclib did not induce G1 cell cycle arrest in cells lacking Rb expression (CDK 4/6-independent mechanism). In combination with chemotherapeutic agents, pretreatment with Trilaciclib attenuated chemotherapy-induced DNA damage in CDK 4/6-dependent cells and dose-dependently reduced chemotherapy-induced apoptosis. Thus, G1T28 was well tolerated and did not antagonize the effects of chemotherapy in CDK4/6-independent (no RB-1 inactivation) SCLC tumor models.

1.2.2. Pharmacokinetics

Pharmacokinetic studies in rats and dogs showed that the plasma half-life values of G1T28 in rats and dogs were approximately 4 to 5 hours after a single intravenous dose. Exposure increased with dose, but not always in proportion with the dose administered. Clearance was comparable in each species at all doses tested, indicating linear PK. Following multiple intravenous doses, G1T28 did not accumulate in rat and dog plasma and CYP inhibition studies in pooled human liver microsomes were performed approximately similarly between 8 exposed males and females, and no direct or time-dependent inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 by trilaciclib was observed. Trilaciclib is unlikely to cause drug-drug interactions by inhibiting compound metabolism mediated by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at concentrations below 100 μM.

In vitro inhibition studies using a membrane transporter model system also indicated that DDI with Trilaciclib is unlikely to occur through inhibition of BCRP-, BSEP-, OAT1-, OAT3-, OATP1B1-, MDR1-, MRP1-, MRP2-, or OATP1B3-mediated transport. Trilaciclib inhibited MATE1, MATE2-K, OCT1, and OCT2 in vitro (IC_{50} values of 0.175, 0.071, 0.6, and 0.152 μM, respectively).

1.2.3. Toxicology

The toxicity of IV and oral G1T28 was assessed in single and repeated dose studies in rats and dogs for up to 14 days as well as in a series of in vitro genotoxicity studies. In addition, the compatibility of the G1T28 clinical drug product with human blood was assessed in vitro.

There was no evidence that Trilaciclib could adversely affect central nervous system function at doses up to 25 mg/kg/day; the minimal clinical signs observed were reversible. Although Trilaciclib did inhibit hERG current in vitro at concentrations > 1000 ng/mL, it had no effect on heart rhythm or QTc interval in dogs when administered as a single IV dose up to 45 mg/kg/day (900 mg/m^2/day) or as a daily dose up to 15 mg/kg/day (300 mg/m^2) for 7 days.

Trilaciclib administered IV for 7 days was maximally tolerated at 25 mg/kg/day (150 mg/m^2/day) in rats and 15 mg/kg/day (300 mg/m$^{2/}$day) in dogs, with the primary toxicity profile of all cytopenias involving hematopoiesis and reflecting its expected mechanism of action. These effects on hematopoiesis were reversible following cessation of dosing.

Additional effects of Trilaciclib on lung, liver, and endocrine/female reproductive systems were also observed.

In rats, single very high doses (≥ 75 mg/kg [450 mg/m^2] bolus and ≥ 250 mg/kg [1500 mg/m^2] 30-min infusion) were associated with asthma and dyspnea, and necropsy revealed dark spots in the lungs.

The hepatic effects of once-daily Trilaciclib administration included mildly increased ALT and AST levels in female rats (50 mg/kg/day) and mildly increased ALT in dogs without any concomitant changes in AST, bilirubin, serum protein concentration, or histology. Hepatic-related effects were reversible in rats and dogs. In rats, but not dogs, once-daily administration of Trilaciclib resulted in changes affecting only the endocrine and/or reproductive systems of females, particularly decreased ovarian and uterine weights and altered estrous cycles. These effects are reversible and may be secondary to non-specific stress.

Once-daily Trilaciclib administration was associated with occasional swelling or edema at the infusion site in dogs, but not rats. In these cases, extravasation of Trilaciclib dosing solution may cause irritation; however, there are no nonclinical data to suggest that Trilaciclib is a blistering agent.

Trilaciclib did not demonstrate mutagenic potential in a GLP bacterial reverse mutation assay nor did it induce γ-H2AX formation in primary human fibroblasts, suggesting a low risk of genotoxicity in cancer patients.

Triraciclib formulated in glucose 5% (w/v) is well compatible with human blood in vitro even at concentrations much higher than those produced during patient treatment. Trilaciclib did not cause red blood cell lysis at any concentration tested (up to 2.5 mg/mL). Trilaciclib caused flocculation of plasma proteins at concentrations ≥ 2.5 mg/mL, but not at concentrations ≤ 0.1 mg/mL. Please refer to the Investigator 's Brochure for more information.

1.3. Clinical data

This study is intended to enroll patients with extensive stage small cell lung cancer (ES-SCLC). The following subsections mainly summarize the clinical data of three clinical trials of Trilaciclib in ES-SCLC patients in western countries (G1T28-02, G1T28-05, G1T28-03). The data of other clinical trials are detailed in the Investigator 's Brochure. The study designs for the three clinical trials are shown in Table 2:

Table 2 Details of Three Clinical Trials of Trilaciclib in Patients with Small Cell Lung Cancer

Trial No./Title	Enrolled Population	Study Design	Study objectives
G1T28-02 Phase 1b/2a Safety and Pharmacokinetic Study of G1T28 (Trilaciclib) in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC) Receiving Etoposide and Carboplatin Chemotherapy.	Patients with newly diagnosed extensive stage SCLC; Part I:19 patients enrolled; Part II:77 randomized patients: • Placebo: 38 patients • Trilaciclib: 39 patients	Part I (Phase 1b/2a): Single-arm open-label dose-finding study of Trilaciclib administered IV QD on Days 1 through 3 of each 21-day EC regimen treatment cycle (Trilaciclib dose started at 200 mg/m^2 and was escalated or de-escalated as needed). Part II: Trilaciclib or placebo IV QD 1:1 randomized double-blind. Trilaciclib 240 mg/m^2 or placebo will be administered intravenously on Days 1-3 of each cycle prior to chemotherapy administration. Chemotherapy - carboplatin administered on Day 1 of each cycle at a target AUC = 5 (maximum dose not to exceed 750 mg); etoposide 100 mg/m^2 administered on Days 1-3 of each cycle	Part I: • Evaluate DLTs; • Identify the recommended clinical phase 2 dose; • Safety and tolerability; • Assess PK profile of G1T28, EC Part II: • To assess myeloprotective endpoints; • Safety and tolerability; • Assess anti-tumor efficacy
G1T28-05 Phase II Clinical Trial of Carboplatin, Etoposide, Atislizumab Combined with Trilaciclib or Placebo in Newly Diagnosed Extensive Stage Non-Small Cell Lung Cancer	Patients with newly diagnosed extensive-stage SCLC; 105 patients randomized 1:1	Randomized double-blind 1:1 treatment or placebo. Treatment Arm: Trilaciclib combined with EC regimen and atezolizumab administered intravenously at 240 mg/m^2 before chemotherapy on Days 1-3 of each cycle of Trilaciclib; maintenance with atezolizumab alone after Cycle 4; Control group: placebo combined with EC regimen and atezolizumab, placebo administered as Trilaciclib in cycles 1-4;	• To assess the myeloprotective effect of Trilaciclib in patients with extensive stage small cell lung cancer treated with EC regimen; • Evaluate safety and tolerability; • Evaluate anti-tumor efficacy

Trial No./Title	Enrolled Population	Study Design	Study objectives
		afatinib monotherapy for maintenance treatment after cycle 4; Chemotherapy - carboplatin administered on Day 1 of each cycle at a target AUC = 5 (maximum dose not to exceed 750 mg); etoposide 100 mg/m^2 administered on Days 1-3 of each cycle	
G1T28-03 Phase Ib/IIa Clinical Study to Evaluate the Safety and Pharmacokinetic Characteristics of G1T28 (Trilaciclib) in Patients with Previously Treated Extensive-Stage Small Cell Lung Cancer Treated with Topotecan	Patients with previously treated (2nd/3rd line) extensive stage small cell lung cancer were enrolled. Part I:32 patients; a total of 90 patients were enrolled in Part II.	Part I: Single-arm, open-label dose-finding trial, Trilaciclib was administered intravenously on Days 1-5 of each cycle before chemotherapy (topotecan) at a starting dose of 200 mg/m^2, which was increased or decreased according to the actual situation. Part II was a randomized double-blind trial with 2:1 allocation. Part IIa: Trilaciclib 240 mg/m^2 or placebo administered as an intravenous infusion before topotecan (0.75 mg/m^2) on Days 1-5 of each 21-day cycle; Part IIb: Trilaciclib 240 mg/m^2 or placebo administered intravenously before topotecan (1.5 mg/m^2) on Days 1-5 of each 21-day cycle;	Part I: • DLTs; • RP2D; • Safety and tolerability Part II: • Myeloprotective endpoints; • Anti-tumor efficacy; • PK profiles of Trilaciclib and Topotecan

1.3.1. Safety data

Exposure:

Overall, 435 individuals (168 healthy subjects and 267 cancer patients) have been exposed to Trilaciclib at various doses and over time: Note that since a small proportion of the same patients were included in Study G1T28-02 and Study G1T28-03 and their safety data in each study are considered separate patient records, a total of N = 272 cancer patients are reported in the Summary of Safety. Cancer patients were treated for a median duration of 4 cycles and 8.8% of patients received more than 10 cycles. Trilaciclib has been evaluated at doses between 6 and 700 mg/m^2. The sample size and duration of exposure in these trials provided an adequate safety database to assess the safety of Trilaciclib administered as a single agent (in healthy subjects) as well as with various chemotherapeutic agents (in cancer patients).

In the SCLC Safety Analysis Set, patients treated with Trilaciclib prior to chemotherapy were more able to receive the recommended dose on time than patients treated with placebo. This improvement was reflected in fewer dose reductions and higher relative dose intensity of chemotherapy administered in the Trilaciclib + Chemotherapy arm compared to the Placebo + Chemotherapy arm.

The percentage of patients who may discontinue treatment due to treatment-emergent adverse events (TEAEs), death, and investigator judgment was lower in patients receiving Trilaciclib than in patients receiving placebo.

Treatment-Emergent Adverse Events:

In the SCLC Safety Analysis Set, a significantly lower percentage of patients treated with Trilaciclib (59.8%) experienced Grade ≥ 3 TEAEs compared with patients treated with placebo (83.1%);

In the SCLC Safety Analysis Set, a significantly lower percentage of patients treated with Trilaciclib (44.3%) experienced Grade 3 or 4 hematologic TEAEs compared with patients treated with placebo (77.1%);

In the SCLC Safety Analysis Set, TEAEs that occurred in ≥ 5% of patients treated with Trilaciclib and at a ≥ 2% higher occurrence than placebo included fatigue (33.6% and 27.1% in the Trilaciclib + Chemotherapy and Placebo + Chemotherapy arms, respectively), pyrexia (13.9% and 11.0%), headache (13.1% and 9.3%), hypokalemia (10.7% and 5.9%), infusion-related reaction (8.2% and 1.7%), upper abdominal pain (6.6% and 2.5%), peripheral edema (6.6% and 4.2%), rash (6.6% and 4.2%), and hyperglycemia (5.7% and 3.4%);

Serious TEAEs were reported in 28.7% of patients receiving Trilaciclib. No preferred term

(PT) had a TEAE occurrence of more than 5% in the overall Trilaciclib + Chemotherapy arm, and the only serious TEAE with an occurrence of 4% was pneumonia. Only 2 patients experienced serious TEAEs related to Trilaciclib (deep vein thrombosis and thrombophlebitis);

In the SCLC Safety Analysis Set, the percentage of patients who discontinued any study drug due to a TEAE was lower in the Trilaciclib + Chemotherapy arm (9.0%) than in the Placebo + Chemotherapy arm (11.0%). Among the 12 patients treated with Trilaciclib who experienced TEAEs related to Trilaciclib that led to discontinuation of any investigational product, only 2 patients had TEAEs related to Trilaciclib only and not to chemotherapy, 1 patient had a Grade 2 infusion-related reaction and 1 patient had a Grade 2 injection site reaction;

Grade 5 TEAEs occurred in 2.9% of cancer patients treated with Tralaciclib at any dose in any study, none were associated with Trilaciclib, and all were consistent with underlying disease and cytotoxic chemotherapy.

1.3.2. Pharmacokinetic data

Trilaciclib was administered as an intravenous infusion at 100% bioavailability and was moderately bound to human plasma proteins (69.6% to 71.7%) and essentially independent of concentration (from 0.05 to 20 μg/mL, including treatment-related concentrations). Trilaciclib is extensively metabolized in humans mainly by CYP3A4, and the main route of metabolism in humans is oxidation (oxidation or N-dealkylation or a combination of both), which is mainly excreted in feces (79.1%).

Following single-dose administration to healthy subjects, C_{max} increased in a dose-proportional manner with AUC slightly greater than dose-proportional over the dose range of 6-192 mg/m^2 (Study G1T28-1-01). At doses of 200 to 700 mg/m^2, increases in C_{max} were approximately dose proportional, while increases in AUC were slightly greater than dose proportional (Study G1T28-11).

Repeated doses of Trilaciclib at doses ranging from 200 to 280 mg/m^2 were assessed for PK in cancer patients. Trilaciclib did not accumulate following repeated once-daily dosing of 240 mg/m^2 for 4 days, with geometric mean accumulation ratios estimated to be 0.917 (124% CV) for C_{max} and 1.05 (42.1% CV) for AUC (Study G1T28-03). At 240 mg/m^2, concentrations of trilaciclib were approximately 1% of C_{max} within 24 hours of dosing; therefore, accumulation following repeated dosing was expected to be minimal and steady state was achieved by Day 1 of trilaciclib dosing.

There were no apparent differences in the PK of Trilaciclib between healthy subjects and patients receiving chemotherapy. On Day 1 of treatment, exposure parameters (AUC and C_{max})

in cancer patients were similar to healthy subjects receiving the equivalent dose of Trilaciclib. Between-subject variability (geometric coefficient of variation [CV]) was moderate in healthy subjects (~ 26% to 53% for C_{max} and ~ 13% to 26% for AUC) and moderate to high in cancer patients (~ 28% to 287% for C_{max} and ~ 19% to 75% for AUC) at doses near or equal to the recommended therapeutic dose of 240 mg/m^2.

Trilaciclib was primarily metabolized by CYP3A4 as assessed in vitro and demonstrated mechanistic, time-dependent inhibition of CYP3A4. Trilaciclib is unlikely to inhibit the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, or to induce the activity of CYP1A2, CYP2B6, or CYP3A4 at therapeutically relevant concentrations. Trilaciclib inhibits OCT2, MATE1, and MATE2-K and is unlikely to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, and OAT3 at clinically relevant concentrations. Based on the in vitro results, clinical trials were performed in healthy subjects to detect clinically relevant DDI mediated by CYP3A4, MATE, or OCT2. The results showed that the therapeutic dose of Trilaciclib was not expected to affect the exposure of co-administered CYP3A substrates and no dose adjustment of CYP3A substrates is recommended (Study G1T28-106); no dose adjustment of Trilaciclib is required when itraconazole or other CYP3A inhibitors are co-administered (Study G1T28-09 and Study G1T28-114); no dose adjustment is required when Trilaciclib is co-administered with rifampicin or other CYP3A inducers (Study G1T28-106). Trilaciclib increased plasma concentrations of metformin by inhibiting OCT2 and/or MATE transporters, but no dose adjustment is required when metformin is combined with trilaciclib since the dosing regimen of trilaciclib is intermittent and the predicted clinical significance of increased plasma concentrations of metformin is modest (Study G1T28-106). Trilaciclib had no effect on the PK of etoposide, carboplatin, topotecan, and gemcitabine, nor on the pharmacokinetics of trilaciclib (Study G1T28-02, Study G1T28-03, Study G1T28-04, and Study G1T28-05).

Trilaciclib has a wide therapeutic window. Efficacy E-R analysis showed a flat pharmacodynamics-exposure profile. Doses administered between 200 and 280 mg/m^2 were consistently associated with desirable responsiveness, including myeloprotective efficacy, exposure associated with nadir neutrophil (ANC), occurrence of severe neutropenia, and occurrence of Grade 3/4 anaemia. Taking into account the difference in drug exposure between subjects, the recommended clinical dose is 240 mg/m^2, which is the middle of the dose range of 200 to 280 mg/m^2. Adverse reactions (including headache, phlebitis/thrombophlebitis, and injection site reactions) ranged from 28.6% (12/42), 7.1% (3/42), and 11.9% (5/42) in the placebo group at cumulative exposure to Trilaciclib of 14.6 to 28.2 μg.h/mL (1/3 higher quartile

of exposure), and 11.5% (17/148), 0.7% (1/148), and 3.4% (5/148) in the placebo group, respectively. With the exception of 1 case of Grade 3 thrombophlebitis, all adverse events were Grade 1 or 2 and were of no practical clinical relevance and no dose adjustment of Trilaciclib was required.

The effect of intrinsic factors on the PK of Trilaciclib was assessed by popPK analysis, including a thorough analysis of covariates. Data collected from healthy subjects (Studies G1T28-1-01 and G1T28-11) and patients with SCLC or TNBC (Studies G1T28-02, G1T28-03, G1T28-05, and G1T28-04) were analyzed combined. The analysis showed no clinically meaningful effect of age, sex, weight, and race on Trilaciclib exposure.

Trilaciclib has not been studied in pediatric patients. The results of the Japanese PK bridging study (Study G1T28-17) showed that the safety and tolerability were good at doses ranging from 100 to 240 mg/m^2 in Japanese subjects, the pharmacokinetic behavior was approximately linear, and the AUC and C_{max} increased slightly more than dose-proportionally. AUC was approximately 30% higher in Japanese subjects compared to non-Japanese subjects, while C_{max} was 2-fold higher, and AUC at 200 mg/m^2 was similar between Japanese and non-Japanese subjects at 240 mg/m^2. At the same dose of 240 mg/m^2, the occurrence of adverse events was similar between Japanese and non-Japanese subjects, and the safety and tolerability of trilaciclib were not significantly different between the two populations. At a single dose of 240 mg/m^2 in Japanese subjects, mean exposure was 4.26 μg.h/mL and was not expected to exceed 14.6 to 28.2 μg.h/mL for 3 to 5 consecutive days (1/3 higher quantile of exposure in the E-R analysis). Based on the exposure-response relationship from previous studies and the safety results from this study, no clinically significant differences in exposure were shown and no dose adjustment is recommended for Japanese subjects.

Less than 2% of the dose of Trilaciclib was excreted unchanged in urine (Study G1T28-1-01), and approximately 14% of drug-related material was excreted via the kidneys (Study G1T28-08). Both studies suggest that renal exclusion is not a major route of exclusion in humans. Based on popPK analysis, including 45 patients with mild renal impairment and 16 patients with moderate renal impairment, mild and moderate renal impairment had no impact on Trilaciclib exposure, and no dose adjustment is required for patients with mild or moderate renal impairment. Trilaciclib has not been studied in patients with severe renal impairment, end-stage renal disease, or dialysis.

Investigations into hepatic impairment are ongoing (Study G1T28-113). Mild hepatic impairment had no impact on Trilaciclib exposure based on popPK analysis including 30

patients with mild hepatic impairment. No dose adjustment is required in patients with mild hepatic impairment. Trilaciclib has not been studied in patients with moderate or severe hepatic impairment.

1.3.3. Efficacy data

Trilaciclib efficacy refers to the prevention of chemotherapy induced bone marrow suppression. A summary of myeloprotective endpoint measures for the three clinical trials conducted in SCLC patients is presented in Table 3. The trial results showed that Trilaciclib had a significant effect in preventing bone marrow suppression, supporting the conduct of a Phase 3 clinical study based on this data in China to evaluate the safety and efficacy of Trilaciclib in Chinese patients.

Table 3 Summary of Trilaciclib Bone Marrow Protection Endpoint Data from Three Clinical Trials in SCLC

Endpoint	Study G1T28-02 Part II			Study G1T28-05			Study G1T28-03 Part II			Integrated Analysis		
	Plac + E/C (N = 38)	Trila + E/C (N = 39)	P value	Plac + E/C/A (N = 53)	Trila + E/C/A (N = 54)	P value	Plac + TPT 1.5 mg/m^2 (N = 29)	Trila + TPT 1.5 mg/m^2 (N = 32)	P value	Placebo + Chemotherapy (N = 119)	Trilaciclib + Chemotherapy (N = 123)	P value
Cycle 1 DSN, mean (SD)	3 (3.9)	0 (0.5)	< 0.0001	4 (4.7)	0 (1.0)	< 0.0001	7 (6.2)	2 (3.9)	< 0.0001	4 (5.1)	0 (1.8)	< 0.0001
Occurrence of severe neutropenia, N (%)	16 (42.1)	2 (5.1)	0.0049	26 (49.1)	1 (1.9)	< 0.0001	22 (75.9)	13 (40.6)	0.016	63 (52.9)	14 (11.4)	< 0.0001
G-CSF use rate, N (%)	24 (63.2)	4 (10.3)	0.0003	25 (47.2)	16 (29.6)	0.0686	19 (65.5)	16 (50.0)	0.2544	67 (56.3)	35 (28.5)	< 0.0001
Occurrence of febrile neutropenia TEAEs, N (%)	3 (7.9)	1 (2.6)	0.4544	3 (5.7)	1 (1.9)	NE	5 (17.2)	2 (6.3)	NE	11 (9.2)	4 (3.3)	0.0889
Occurrence of RBC transfusion in Cycle 5 and beyond, N (%)	9 (23.7)	2 (5.1)	0.0338	11 (20.8)	7 (13.0)	0.1335	12 (41.4)	10 (31.3)	0.3222	31 (26.1)	18 (14.6)	0.0252
Number of Red Blood Cell Transfusion Events on/after Week 5 (Weekly Occurrence)	0.019	0.005	0.0208	0.026	0.017	0.1954	0.063	0.026	0.0302	0.031	0.015	0.0027
Erythropoiesis StimulatingAgent Use, N (%)	2 (5.3)	1 (2.6)	NE	6 (11.3)	3 (5.6)	0.3343	6 (20.7)	1 (3.1)	0.0673	14 (11.8)	4 (3.3)	0.0254
Number of Erythropoiesis Stimulating Agents Used (Events Per Week)	0.021	0.016	0.4368	0.06	0.026	0.2412	0.143	0.059	0.1228	0.064	0.016	0.0359
Occurrence of Grade 3/4 Decreased Hemoglobin Levels, N (%)	7 (18.4)	4 (10.3)	0.1682	15 (28.3)	10 (18.5)	0.2369	17 (58.6)	12 (37.5)	0.093	38 (31.9)	25 (20.3)	0.0279
Occurrence of platelet transfusion, N (%)	0	2 (5.1)	NE	2 (3.8)	1 (1.9)	NE	9 (31.0)	8 (25.0)	0.3222	11 (9.2)	10 (8.1)	0.9564

Endpoint	Study G1T28-02 Part II			Study G1T28-05			Study G1T28-03 Part II			Integrated Analysis		
	Plac + E/C (N = 38)	Trila + E/C (N = 39)	P value	Plac + E/C/A (N = 53)	Trila + E/C/A (N = 54)	P value	Plac + TPT 1.5 mg/m^2 (N = 29)	Trila + TPT 1.5 mg/m^2 (N = 32)	P value	Placebo + Chemotherapy (N = 119)	Trilaciclib + Chemotherapy (N = 123)	P value
Number of platelet transfusions (events per week)	0	0.008	0.4539	0.007	0.002	0.7017	0.063	0.028	0.7386	0.017	0.011	0.5169
Occurrence of Grade 3/4 platelet count decreased, N (%)	5 (13.2)	4 (10.3)	0.4572	20 (37.7)	1 (1.9)	0.0031	19 (65.5)	21 (65.6)	0.9306	43 (36.1)	24 (19.5)	0.0067
Occurrence of All Causality Chemotherapy Dose Reductions, N (%)	13 (34.2)	3 (7.7)	0.0156	14 (26.4)	3 (5.6)	0.0127	9 (31.0)	6 (18.8)	0.204	36 (30.3)	11 (8.9)	< 0.0001
Number of All Causality Chemotherapy Dose Reductions (Events Per Week)	0.084	0.022	0.0189	0.085	0.021	0.0195	0.116	0.051	0.1913	0.093	0.028	< 0.0001
Occurrence of serious infection TEAEs, N (%)	2 (5.3)	4 (10.3)	0.2965	7 (13.2)	3 (5.6)	0.2644	3 (10.3)	1 (3.1)	NE	12 (10.1)	8 (6.5)	0.4152
Occurrence of intravenous antibiotics, N (%)	8 (21.1)	8 (20.5)	0.7154	12 (22.6)	10 (18.5)	0.8196	8 (27.6)	7 (21.9)	NE	28 (23.5)	24 (19.5)	0.6207

Notes: E-etoposide, C-carboplatin, TPT: topotecan, Trila-Trilaciclib, A-atezolizumab, plac- placebo

1.4. Risks and benefits

In summary, CIM remains an urgent unmet clinical need. Some symptomatic treatments for myelosuppression (e.g., blood transfusions, growth factors, etc.) are available, but the treatment options are limited, and each therapy carries its own additional risks. Currently, there are no effective treatments that can prevent CIM before chemotherapy causes damage, thereby improving the overall safety of cancer patients. As the first agent designed to reduce CIM by protecting HSPC, Trilaciclib showed a strong ability to prevent or alleviate CIM in patients with extensive stage small cell lung cancer (ES-SCLC). The risk-benefit assessments of the current data for Trilaciclib support the first clinical study application in China: prophylactic use of Trilaciclib to improve CIM in patients with ES-SCLC receiving platinum plus etoposide or topotecan. The sponsor will conduct a clinical study including an open-label safety run-in and PK evaluation part and a randomized double-blind, placebo-controlled study part to assess the safety, efficacy, and pharmacokinetic profile of Trilaciclib in combination with EC or topotecan in ES-SCLC to support the marketing of Trilaciclib in China for this indication.

2. Study objective and study endpoints

2.1. 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.

2.2. Study endpoints

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 chemotherapy dose reductions;
  - Febrile neutropenia;
  - SN prolongation (lasting > 5 days);
  - RBC transfusion 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) use rate;
- Recombinant human interleukin -11 use rate;
- Thrombopoietin (TPO) use;
- Occurrence of intravenous or oral antibiotic administration;
- Occurrence of infectious serious adverse events;
- Occurrence of serious adverse events of lung infection;
- 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 chemotherapy dose reductions;
  - Febrile neutropenia;
  - SN prolongation (lasting > 5 days);
  - RBC transfusion 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) use rate;
- Rate of recombinant human interleukin -11 use;
- Thrombopoietin (TPO) use;
- 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.

3. Study design

3.1. Overall 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 is safety run-in and PK evaluation, about 12 patients with extensive stage small cell lung cancer, 6 patients with 1st line ES-SCLC and 6 patients with 2nd/3rd line ES-SCLC were enrolled and treated with Trilaciclib in combination with carboplatin and etoposide or with topotecan, respectively, and based on evaluable data from cycle 1, the safety, tolerability, pharmacokinetics, and preliminary efficacy (prevention of myelosuppression) of Trilaciclib were evaluated. The second part 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. Trilaciclib was administered at a planned dose of 240 mg/m^2 , and 12 additional patients (6 each for 1st line ES-SCLC and 2nd/3rd line ES-SCLC) were to be enrolled in Part I to explore the PK and safety of Trilaciclib 200 mg/m^2 if safety data from Part I of the study suggested that a dose adjustment of Trilaciclib was required.

Patients meeting the inclusion and exclusion criteria will receive the following treatments:

Patients with first line ES-SCLC: Trilaciclib 240 mg/m^2 administered intravenously once daily prior to chemotherapy on Days 1 to 3 of each 21-day cycle; carboplatin dose will be calculated according to Calvert formula as target AUC = 5 (maximum 750 mg) on Day 1 and 100 mg/m^2 etoposide administered intravenously daily on Days 1-3. Patients will receive up to 6 cycles or until disease progression, intolerability, withdrawal of consent, or investigator termination of treatment, whichever occurs first.

Patients with 2nd/3rd line ES-SCLC: Trilaciclib 240 mg/m^2 IV daily on Days 1 to 5 of each 21-day cycle prior to chemotherapy; Topotecan 1.25 mg/m^2 on Days 1-5 of each cycle. Study drug will be administered until disease progression, intolerability, withdrawal of consent, or investigator termination of treatment, whichever occurs first.

The study process includes screening period, treatment period, safety follow-up and survival follow-up.

3.2. 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 ES-SCLC patients (approximately 40 per arm).

3.3. Rationale for trial design

Trilaciclib has conducted a number of clinical studies in the United States and Europe, all clinical trials were conducted according to standard operating procedures of the sponsor and/or contract research organization in compliance with Good Clinical Practice for the design, conduct, and analysis of clinical trials. All trials were conducted with the approval of the local

ethics committee or institutional review board. Among them, three randomized, double-blind phase II clinical trials in patients with small cell lung cancer (SCLC) confirmed that Trilaciclib administered in combination with chemotherapy (including 1st and 2nd/3rd lines of chemotherapy) can prevent or reduce chemotherapy-induced myelosuppression.

Based on the results of the clinical trials completed overseas, Trilaciclib has clear target of action, clear pharmacological action, good safety and tolerability, moderate protein binding rate, less DDI, intravenous administration is not affected by dietary absorption, and there is no significant difference in PK behavior between cancer subjects and healthy subjects. The exposure of Trilaciclib is found to be slightly higher in the Japanese population than in the European and American populations. Based on its good safety and tolerability and exposure-efficacy relationship, it is considered that the exposure difference has no significant clinical significance, and dose adjustment is not recommended. Efficacy E-R analysis showed a flat pharmacodynamics-exposure profile. Doses administered between 200 and 280 mg/m^2 resulted in desirable responsiveness, including myeloprotective efficacy (exposure associated with ANC, severe neutropenia, and anemia occurrence) and antitumor activity (ORR, PFS, and OS). Taking into account the difference in drug exposure between subjects, the recommended clinical dose is 240 mg/m^2, which is the middle of the dose range of 200 to 280 mg/m^2. The E-R analysis of safety showed that the higher the exposure, the greater the probability of headache, phlebitis/thrombophlebitis, and injection site reactions, but these adverse reactions were of low grade and not clinically significant. Chinese and Japanese belong to Asian race, and the safety, exposure and efficacy of Trilaciclib in Chinese are expected to be similar to those in Japanese, supporting the safety and efficacy of this product in Chinese observed at the dose level of 240 mg/m^2.

Trilaciclib has demonstrated efficacy and safety. At present, there is no evidence that the response of Chinese patients to drug treatment is different from that of overseas populations and may bring about safety and effectiveness impact.

At present, there is no relevant data on the use of Trilaciclib in the Chinese population in clinical trials of Trilaciclib. Therefore, in order to further evaluate the safety and efficacy of Trilaciclib in Chinese patients, a clinical trial including an open-label safety run-in and PK evaluation part and a randomized double-blind, placebo-controlled part is planned to be conducted in extensive stage small cell lung cancer in China.

3.4. End of study

The end of the study is defined as follows:

75% of subjects died, or 12 months after the last subject was enrolled, or the sponsor decided to terminate the study, whichever came first.

4. Study population

The proposed study population is patients with extensive stage small cell lung cancer.

4.1. Criteria for enrollment

Criteria for enrollment

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 ≥ 1.5×10^9/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.

4.2. 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.

5. Investigations treatment

5.1. Investigational drug

The study drug in this trial is: Trilaciclib/placebo, and the chemotherapy drugs for combination therapy are carboplatin, etoposide or topotecan.

Investigational product investigated:

Trilaciclib: provided by Jiangsu Simcere Pharmaceutical Co., Ltd., 300 mg/vial. Trilaciclib is a sterile powder, USP D-mannitol is added as cake formers, and citrate buffer is added to maintain the pH of the reconstitution at 4.0 to 5.0. The preparation of the study drug for reconstitution and dilution is described in detail in the Pharmacy Manual.

Trilaciclib placebo: The outer box of the placebo is designed to be consistent with the investigational product, Trilaciclib, and the contents of the box are filled with the same quality of padding (paper sheets), which will not break blind in appearance or handheld after sealing.Placebo was actually used to prepare 250 mL of 5% dextrose in water or saline (0.9% sodium chloride) as the vehicle used for Trilaciclib.

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

The structure and other pharmaceutical properties of chemotherapeutic drugs are detailed in the corresponding package inserts.

5.2. Study treatment regimen

The treatment regimen for this study is as follows:

Patients with 1st line ES-SCLC were treated with Trilaciclib or placebo in combination with carboplatin and etoposide (EC regimen); patients with 2nd/3rd line ES-SCLC were treated with Trilaciclib or placebo in combination with topotecan as detailed in Table 4 below:

Table 4 Study Treatment Regimen

Investigational drug		Usage	Period of administration
1st line ES-SCLC			
EC Regimen	Carboplatin	Target AUC = 5 (maximum dose 750 mg), intravenous drip over 30 min on Day 1 of each 21-day cycle;	Up to 6 cycles *
	Etoposide	100 mg/m^2, 21 days per cycle, intravenous drip over 60 min on days 1-3;	Up to 6 cycles *
Trilaciclib/Placebo		240 mg/m^2, 21 days per cycle, 30 min intravenous drip before chemotherapy on Days 1-3 (try to complete the drip within 30 + 5 min due to PK study);	Up to 6 cycles *
* OR Progressive disease, intolerable, withdrawal of consent, or investigator discontinuation prior to reaching 6 cycles, whichever came first			
2nd/3rd line ES-SCLC patients			
Topotecan		1.25 mg/m^2, 21 days per cycle, intravenous drip over 30 min on Days 1-5;	Until disease progression, intolerable, withdrawal of consent, or investigator termination of treatment, whichever came first
Trilaciclib/Placebo		240 mg/m^2, 21 days per cycle, administered prechemotherapy over 30 min on Days 1-5 (infusion should be completed within 30 + 5 min if possible due to PK studies).	Until disease progression, intolerable, withdrawal of consent, or investigator termination of treatment, whichever came first

Date of medication visit is based on the first dose of investigational drug (Trilaciclib/Placebo) in each cycle (D1).

Notes:

Trilaciclib should be administered no more than 28 hours apart between infusions for 3 or 5 consecutive days, and no more than 4 hours between infusions of Trilaciclib and its subsequent injected chemotherapeutic agents (carboplatin or etoposide, or topotecan).

Trilaciclib should be used in combination with chemotherapy, that is, if EC regimen or topotecan is suspended or terminated, then trilaciclib should also be suspended or terminated. Similarly, subsequent chemotherapy should not be administered if the planned administration of Trilaciclib, i.e. Trilaciclib or placebo, has not been completed in any cycle.

Prophylactic use of any colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte-giant cell colony-stimulating factor, erythropoiesis stimulating agent) was 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.).

5.3. Randomization and blinding

5.3.1. Randomization and blinding

The first part of the study was divided into open-label studies without randomization and blinding.

The second part of the study was a randomized double-blind study. The investigator will enter the Interactive Web Response System (IWRS) after confirming that the subject meets all inclusion and exclusion criteria. The IWRS will assign a randomization number that associates the subject with a treatment group and assigns a specific treatment to the subject who should receive study treatment within 3 days of randomization, including the day of randomization. Subjects were randomized to Trilaciclib or placebo in a double-blind 1:1 ratio, stratified by 1st line vs 2nd/3rd line ES-SCLC, ECOG PS (0-1 vs 2), and presence vs absence of brain metastases. Investigators involved in the trial (including investigators, sponsor personnel, contract research organization personnel, central pathology reviewer, biological sample analysts, etc., and subjects were blinded to which drug treatment was assigned. The investigator obtained the subject 's assigned randomization number based on the information provided by the IWRS.

Specific blinding procedures are described in the Drug Administration Manual.

5.3.2. Unblinding

Unblinding may be performed in emergency situations. Emergency unblinding should be the last category of measures to deal with emergencies associated with the medication and/or dose administered to the subject. If unblinding is necessary for safety reasons (e.g., serious adverse events, etc.) to treat a subject, it is recommended that the sponsor 's medical monitor be contacted prior to unblinding and the investigator unblinding the subject via the IWRS system. Once unblinded, the subject discontinued study treatment. The investigator should record this event in the original medical records and inform the sponsor 's clinical medical director as soon as possible.

For the purpose of regulatory reporting, the Sponsor PV will unblind the treatment code if required by health authorities for all serious, unexpected suspected adverse events considered related to the study drug by the investigator or sponsor, etc., but the Sponsor study team remains blinded.

In the second part, when the primary analysis is performed for the primary endpoint, the

necessary sponsor personnel will be unblinded and the investigator, subjects and other personnel will continue to be blinded; at the final analysis, the study will be unblinded.

5.4. Study treatment modification

5.4.1. Dose modification for trilaciclib/placebo

Based on previous clinical studies with Trilaciclib and considering that the risk of inadequate HSPC stagnation is minimized as much as possible, the dose of Trilaciclib/placebo will not be adjusted and remains at 240 mg/m^2 in this trial unless safety data in Part I suggest that the dose of Trilaciclib/placebo needs to be adjusted.

Refer to Section 5.5.1.1 for dose interruptions and terminations of Trilaciclib.

5.4.2. Dose modification for chemotherapy agents

Carboplatin, etoposide, and topotecan should meet neutrophil ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L before dosing on the first day of the second and subsequent cycles, and all drug-related nonhematologic toxicities (except alopecia) need to recover to Grade 1 or lower or baseline levels. Dose modifications on the first day of the second and subsequent cycles are shown in Table 5, and 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 the investigator believes that a delay of more than 2 weeks is beneficial to the subject, dosing may be delayed for more than 2 weeks upon request by the investigator and medical review and written approval by the sponsor.

Table 5 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

Note: Simultaneous dose reduction of carboplatin and etoposide is defined as one dose reduction

5.4.2.1. Dose modifications based on hematologic toxicities

Dose modifications were based on various hematologic toxicities occurring during Cycle 2 and on Day 1 of subsequent cycles as follows:

Table 6 Dose Modification Based on Neutrophil Count and Platelet Count

Neutrophil count < 1.5 x 10^9/L	Carboplatin, etoposide and topotecan

First occurrence	Without dose adjustment, G-CSF was used according to the 2019 edition of Expert Consensus on Diagnosis and Treatment of Neutropenia Caused by Cancer Chemotherapy
Second occurrence	First Dose Reduction
Third occurrence	Second Dose Reduction
Fourth occurrence	Drug withdrawn
Platelet count < 100 x 10^9/L	**Carboplatin, etoposide and topotecan**
Second occurrence	First Dose Reduction
Third occurrence	Second dose reduction
Fourth occurrence	Drug withdrawn

Table 7 Dose Modification Based on Absolute Trough Neutrophil Count with or without Fever

Absolute neutrophil count trough	**Carboplatin, etoposide and topotecan**
Grade 3 or 4 < 7 days (no fever)	No dose adjustment
Grade 4 ≥ 7 days (no fever)	
First occurrence	Without dose adjustment, G-CSF was used according to the 2019 edition of Expert Consensus on Diagnosis and Treatment of Neutropenia Caused by Cancer Chemotherapy
Second occurrence	First Dose Reduction
Third occurrence	Second Dose Reduction
Fourth occurrence	Drug withdrawn
Grade 3/4 (fever)	
First occurrence	Without dose adjustment, G-CSF was used according to the 2019 edition of Expert Consensus on Diagnosis and Treatment of Neutropenia Caused by Cancer Chemotherapy
Second occurrence	First Dose Reduction
Third occurrence	Second Dose Reduction
Fourth occurrence	Drug withdrawn

Table 8 Dose Modification Based on Trough Platelet Values

Platelet count	**Carboplatin, etoposide and topotecan**
⩾ Grade 3 combined bleeding or Grade 4	
First occurrence	No dose adjustment, recombinant human interleukin-11, rhIL-11 derivatives, recombinant human thrombopoietin or platelet transfusions were used according to the 2019 Chinese Expert Consensus on Diagnosis and Treatment of Thrombocytopenia Associated with Cancer Chemotherapy
Second occurrence	First Dose Reduction
Third occurrence	Second Dose Reduction
Fourth occurrence	Drug withdrawn

5.4.2.2. Dose Modifications Based on Nonhematologic Toxicities

5.4.2.2.1. Hepatotoxicity

Dose modifications were based on hepatotoxicity occurring on the first day of the second and subsequent cycles as follows:

Table 9 Dose Modifications Based on ALT/AST and Bilirubin

ALT/AST		**Bilirubin**	**Carboplatin, etoposide and topotecan**
Grade 1	**AND/OR**	≤ Grade 2	No change
Grade ⩾ 2 a First occurrence Second occurrence Third occurrence	**AND/OR**	Grade ≥ 3 First occurrence Second occurrence Third occurrence	First Dose Reduction Second dose reduction Drug withdrawn

A If liver metastasis is present at baseline and ALT/AST is Grade 2, a 1-grade worsening of the AE grade will result in a reduction of the first dose. If combined ALT/AST/combined bilirubin abnormalities occur, dose reduction is judged based on more severe cases.

5.4.2.2.2. Gastrointestinal side effects

Antiemetics and antidiarrheals may be used to control nausea, vomiting, and diarrhea. Subjects were encouraged to take large oral rehydration fluids.

5.4.2.2.3. Hypersensitivity

For subjects who experience mild to moderate hypersensitivity reactions and have been successfully managed, prophylaxis and bedside vital sign monitoring is recommended for all

subsequent doses.

- Mild symptoms (eg, mild flushing, rash, itching): complete the infusion. Bedside monitoring. No treatment required.
- Moderate symptoms (eg, moderate rash, flushing, mild dyspnea, chest discomfort): discontinue infusion. Diphenhydramine 25 mg and dexamethasone 10 mg were administered intravenously. The infusion was resumed at a low rate (20 mg/h) after recovery of symptoms. If no further symptoms appear after 15 min, the rate may be increased to full rate until the infusion is complete. If symptoms recur, the infusion must be stopped. Subjects should not receive additional chemotherapy during this cycle, but may receive doses for subsequent cycles at the investigator 's discretion.
- Serious life-threatening symptoms (eg, hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilator therapy, generalized urticaria): discontinue infusion immediately. Diphenhydramine and dexamethasone were administered intravenously as described above. Adrenaline or bronchodilators were added if needed. Epinephrine is recommended if wheezing is present that is not responsive to bronchodilators. Subjects should not receive any further doses of etoposide or carboplatin. This event was reported as an adverse event.

5.4.2.3. Other toxicities

For the first occurrence of any nonhematologic Grade 2 chemotherapy-related toxicity (except alopecia), all study treatment should be withheld until the toxicity recovers to Grade 1 or baseline. Treatment may then be resumed at the same dose level. For the second occurrence of any nonhematologic Grade 2 chemotherapy-related toxicity (except alopecia), treatment should be resumed at a reduced dose level following recovery of the toxicity to Grade 1 or baseline; for the third occurrence, the dose should be reduced to Dose Level 2. A fourth occurrence will lead to discontinuation of carboplatin, etoposide and topotecan treatment. For Grade 1 toxicities, the dose should not be reduced.

For any Grade 3 or 4 chemotherapy-related toxicity not mentioned above, all study treatments should be withheld until the toxicity recovers to Grade 1 or baseline. Treatment should then be resumed at the first appearance with the first dose reduction and at the second

appearance with the second dose reduction. A third occurrence will lead to discontinuation of carboplatin, etoposide and topotecan treatment.

The above chemotherapy drug dose adjustment regimen is recommended by the study. If the investigator recommends different treatments in clinical practice, the investigator may select the adjustment regimen by referring to the corresponding package insert of chemotherapy drugs or clinical routine guidelines. In this case, it is necessary to clearly record the reasons for other adjustment regimens in the subject 's case and discuss with the sponsor if necessary.

5.5. Criteria for discontinuation from study treatment or withdrawal

5.5.1. 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 should be followed up according to the protocol.

5.5.1.1. Dose interruption and termination of trilaciclib

For adverse events of special interest defined in Protocol Section 8.9, refer to Investigator 's Brochure Section 6 .2 to determine whether to stop the infusion or interrupt t rilaciclib treatment. Adverse events of special interest for which no action was given in the Investigator 's Brochure were handled as defined below:

- Other Toxicity Events: For severe (Grade 3) other toxicity events, hold Trilaciclib until the event recovers to ≤ Grade 1 or baseline, then consider resuming Trilaciclib; if Grade 3 events recur, permanently discontinue Trilaciclib. Trilaciclib was permanently discontinued for life-threatening (Grade 4) other toxicities.
- Hepatotoxicity: refer to treatment for "other toxic reactions" above.
- Embolic/Thrombotic Events, Venous: if related to the injection site, refer to Chapter 6 .2, "Injection site reaction/phlebitis/thrombophlebitis" of the Investigator 's Brochure; if not related to the injection site, refer to "Other toxicities" as described above.

5.5.2. 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.

5.5.3. Handling of study treatment discontinuation or early withdrawal

When a subject discontinues study treatment or prematurely withdraws, the reason for discontinuation/early withdrawal (the primary reason should be provided if there are multiple reasons) should be documented in the original medical record and CRF, and unused study drug must be counted and returned. When the subject is lost to follow-up, the investigator should make every effort to reach out to the subject (telephone, mail/letter, contact relatives and friends according to registered information) and record these processes in the relevant documents.

5.5.4. 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.

5.6. Prior/concomitant medications and therapies

All concomitant medications, including prescription drugs, over-the-counter preparations, growth factors, blood products, and parenteral nutrition, were documented during the study treatment period and safety follow-up period within 14 days prior to informed consent. Documentation will include information on start and stop dates, dose, and reason for use.

During the study period, no other anticancer therapies other than those specified in this protocol, including Chinese herbal medicines with antitumor activity, are allowed before disease progression.

During the study (treatment period and safety follow-up period), participation in other interventional investigational product clinical trials is not allowed.

Extreme care should be taken when etoposide phosphate is used with drugs known to inhibit phosphatase activity, such as levamisole hydrochloride. Although carboplatin nephrotoxicity is not significant, extra care should be taken when carboplatin is combined with aminoglycosides, which increases renal and/or auditory toxicity. Etoposide or any drug contraindicated with carboplatin is prohibited and special warnings and precautions in the instructions for use of carboplatin and etoposide should be observed.

Necessary supportive treatments such as antiemetics, antidiarrheals, etc. were permitted. Prophylactic use of colony-stimulating factors and hematopoietic growth factors during Cycle 1 is not permitted (ie, no growth factors should be used prophylactically in principle until the actual Cycle 2 Day 1 dose follow-up). However, the use of colony-stimulating factors and hematopoietic growth factors in subsequent cycles and, if necessary, therapeutic use in Cycle 1 may be decided at the discretion of the investigator.

The PK characteristics of subjects should be evaluated in Part I of the study. In order not to affect the metabolism of Trilaciclib, subjects in Part I should not take concomitant strong or moderate inducers of CYP3A4 within 4 weeks before administration of the study drug, strong inhibitors of CYP3A4 within 2 weeks before administration of the study drug, and strong or moderate inducers and strong inhibitors of CYP3A4 before the end of PK blood sampling in

Part I. Common inhibitors and inducers of CYP3A4 are detailed in Appendix 2.

Hematopoietic growth factors, transfusions, or platelet transfusions were prohibited within 1 week prior to the Screening blood tests.

Any diagnostic, therapeutic or surgical procedures performed during the study should be documented. Documentation will include information on dates, indications for use, procedure instructions, and any clinical or pathologic findings. Medications will be coded using the latest World Health Organization (WHO) Drug Dictionary version.

6. Pharmacokinetics

PK pharmacokinetics will be investigated in this study.

6.1. Collection, processing and storage of biological samples

6.1.1. PK Blood Sample Collection and Processing

6.1.1.1. PK blood sample collection time

6.1.1.1.1. Pharmacokinetic evaluation (Part I)

In the first part of this study, PK blood samples will be collected at the following time points.

When chemotherapy regimen is carboplatin combined with etoposide (EC regimen):

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 prior to 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 prior to 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 prior to 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.

6.1.1.1.2. Pharmacokinetic evaluation (Part II)

In the second part of this study, PK blood sample collection is planned to be performed at the following time points, and the actual blood collection points could be adjusted according to the pharmacokinetic study results in the first part.

In all subjects, venous blood is collected at 4 blood sampling points on Cycle 1 Day 1 immediately after the end of Trilaciclib/placebo infusion (excluding flushing time) ± 5 min, 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 for pharmacokinetic analysis according to the test results.

6.1.1.2. Handling and storage of pk blood samples

Please refer to the laboratory manual.

7. Study evaluation

7.1. Evaluation of bone marrow protection

Assessment of myeloprotection will be based on the following: dynamic changes in complete blood counts; hematological toxicities, including febrile neutropenia and resulting infections; red blood cell and platelet transfusions; use of hematopoietic growth factors; systemic antibiotic use; dose reduction and discontinuation of chemotherapy.

Duration of severe neutropenia (DSN) in Cycle 1 was selected as the primary endpoint for efficacy evaluation. The overall protective effect of trilaciclib on each bone marrow cell line 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 endpoints-major adverse hematologic event, etc.).

7.2. Safety evaluation

7.2.1. Clinical laboratory tests

Blood samples for hematology, urinalysis, and blood chemistry will be collected according to the trial flow chart and analytical testing will be completed at a local laboratory.

- Blood routine: 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.;
- Urinalysis: urine protein, urine pH, urine ketone body, urine glucose, urine red blood cells, urine white blood cells, etc. Note: 24-hour urine protein quantification is required for subjects with urine protein $\geqslant$ ++;
- Blood biochemistry: 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);
- Serum pregnancy test (females of childbearing potential only), For female subjects of childbearing potential, serum pregnancy test will be performed before the start of administration. After negative results of pregnancy test in the screening period, reliable contraceptive measures should be started;

  Note: Females who were not of childbearing potential were permanently sterilized

(hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) and postmenopausal. A woman ≥ 50 years of age was considered postmenopausal if she had been amenorrheic for 12 months prior to the planned date of randomization and had no other medical etiology. A woman < 50 years of age is considered postmenopausal if she has been amenorrheic for 12 months or more after stopping exogenous hormone therapy and has follicle-stimulating hormone (FSH) levels in the postmenopausal range.

- Virology:

  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) was positive, HBV-DNA should be added; hepatitis C examination: if hepatitis C antibody was positive, HCV-RNA should be added.

The procedures and timing of these inspections are specified in the Study Flow Chart. Additional laboratory tests may be performed if clinically indicated.

Laboratory test results must be reviewed and confirmed by the investigator or qualified designee.

7.2.2. Physical examination and vital signs

The investigator or other study personnel authorized by the investigator should perform physical examinations and determine the subject 's vital signs as specified in the protocol. Physical examination included weight, height, general appearance, skin/mucous membranes, head, neck, chest, abdomen, joints of spine and limbs, and neurological examination. Height was measured at screening only. Further targeted physical examinations may be performed by the investigator based on symptoms. Vital signs include temperature, pulse, respiratory rate, blood pressure.

7.2.3. 12-lead electrocardiogram (ECG)

Standard 12-lead ECGs, including measurements of heart rate, QRS duration, and PR, QT, RR, and QTc intervals ($QTc = QT/RR^{0.33}$), should be performed using standard procedures at the study site. The timing of ECG measurements was specified in the trial flow chart. Unscheduled ECGs may be performed if clinically indicated.

7.2.4. Adverse events

Adverse events were 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 came earliest. The investigator should record AEs experienced by each subject and

track progress. Adverse events should be graded and documented according to NCI-CTCAE version 5.0 throughout the study and during follow-up.

Details of AE assessment and recording are provided in the relevant sections.

7.3. Pharmacokinetic evaluation

The first part of the pharmacokinetic analysis included PK concentration analysis and PK parameter analysis.

Pharmacokinetic analysis will be based on PK analysis set (PKS), including all subjects who have received at least one dose of study drug and have at least one valid concentration data of the tested components after dosing. Non-compartmental methods using WinNonlin Version 6.3 or higher software were used to calculate pharmacokinetic parameters and descriptive summary analyses were provided.

Single-dose PK parameters:

Peak drug concentration (C_{max}), time to reach maximum concentration (T_{max}), terminal elimination half-life ($T_{1/2}$), area under concentration-time curve (AUC, including AUC_{0-t}, $AUC_{0-\infty}$), etc.

Multiple-dose PK parameters:

Time to maximum concentration (T_{max}), time to maximum concentration at steady state ($T_{ss\,max}$), maximum drug concentration (C_{max}), maximum drug concentration at steady state ($C_{ss\,max}$), minimum plasma concentration at steady state ($C_{ss\,min}$), area under the concentration-time curve (AUC, Including AUC_{0-t}, $AUC_{0-\infty}$, AUC_{ss}), terminal elimination half-life ($T_{1/2}$), fluctuation coefficient (DF), accumulation coefficient (R_{AC}), etc.

7.4. Population pharmacokinetic analysis was performed based on the data obtained for exploratory analysis to obtain the population pharmacokinetic profile of the drug.Antitumor efficacy evaluation

Tumor imaging evaluation was performed according to RECIST1.1.

Pre-screening imaging should include at least computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest, abdomen, and pelvis. Unless contraindicated, IV contrast should be used and oral contrast may be used at the investigator 's discretion.

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 treatment due to intolerable toxicity or for 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), and the sites examined are consistent with the sites examined at baseline.

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.

If there are imaging results meeting the criteria available within 2 1 days prior to the first dose, they do not need to be repeated during the screening period.

For subjects who did not experience disease progression at the time of treatment discontinuation, radiographic tumor assessments continued as scheduled until disease progression, withdrawal of consent, start of subsequent anticancer therapy, or end of study.

8. Adverse event reporting

During this study, the investigator and his/her designated qualified personnel were responsible for detecting and recording all events observed during the course of the study that met the definition of an adverse event or serious adverse event according to the criteria and definitions in this study protocol. Investigators will evaluate adverse events, monitor the safety status of subjects and give corresponding protective measures to ensure the safety of subjects, and report according to relevant requirements.

8.1. Definitions of adverse event, serious adverse event, and suspected and unexpected serious adverse reaction

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered an investigational product and which may manifest as symptoms, signs, disease, or laboratory abnormalities, but which do not necessarily have a causal relationship with the investigational product. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational product.

Events meeting the definition of an adverse event include:

- Abnormal laboratory findings (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiographic scans, vital sign measurements), including those that worsened from baseline and were considered clinically significant

based on the investigator 's medical and scientific judgment (ie, not related to progression of the underlying disease).

- Worsening of a pre-existing condition, including an increase in frequency and/or severity of the condition.
- New conditions detected or diagnosed after the start of the study drug (even if they may have been present before the start of the study).
- Signs, symptoms, or clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of study treatment or concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose with possible suicidal/self-injurious intent. Such overdoses should be reported regardless of sequelae.

Events that do not meet the definition of an adverse event include:

- Abnormal laboratory findings or other abnormal safety assessments related to the underlying disease. However, if the investigator considers the severity to be greater than expected based on the subject 's condition, it should be considered an AE.
- Medical or surgical procedures (eg, endoscopy, appendectomy). Note that the condition leading to this procedure was an AE.
- Absence of an untoward medical event (hospitalization for social reasons and/or convenience).
- Underlying diseases or conditions present or detected at the start of the study that fluctuated daily within the expected range without apparent worsening.
- Pre-existing conditions or signs and/or symptoms not related to the study prior to the first dose of study drug. These events will be documented in the medical history section of the eCRF.
- Progressive Disease (PD): The expected progression of the disease under study occurring during the study is not recorded as an AE or SAE, nor is the sign or symptom caused by the expected disease progression recorded as an AE or SAE. If the investigator considers disease progression related to the investigational product during the study, it should be recorded as AE or reported as SAE; the death caused by disease progression during the safety follow-up period of the subject should be reported as SAE.

Definition of Serious Adverse Event

Serious Adverse Event (SAE) refers to any untoward medical occurrence such as death, life-threatening, permanent or serious disability or incapacity, hospitalization or prolongation of hospitalization required by the subject or congenital anomaly or birth defect after the subject receives the investigational product.

- Causing death
- Life Threatening

This refers to an AE in which the subject was already at risk of death at the time of the AE, and does not refer to an assumption that the AE, if more severe, could have caused death.

- Persistent or significant disability or incapacity

The AE results may cause serious inconvenience or interference with the subject 's normal life and activities.

- Requires hospitalization or prolongation of hospitalization

The AE caused the subject to be hospitalized for treatment or had already been prepared to be discharged, but prolonged hospitalization due to an adverse event; it was necessary to be clear that the cause of the condition was due to the adverse event rather than admission for elective surgery, non-medical reasons, etc.

- Congenital anomaly or birth defect

The offspring of the subject presents with malformation or congenital functional defect.

- Other important medical events

Medical and scientific judgment must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening, fatal, or hospitalised, but medical action to prevent one of the above situations is also usually considered serious. For example, important treatment in the emergency room or allergic bronchospasm at home, cachexia or convulsion without hospitalization, drug dependence or addiction.

When it is unclear whether the SAE is considered, the investigator should discuss with the sponsor and the Ethics Committee.

Definition of suspected and unexpected serious adverse reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) refers to a suspected and unexpected serious adverse reaction whose nature and severity of clinical manifestations exceed

those in the Investigator 's Brochure (IB) of the investigational product, the package insert of the marketed drug or the summary of product characteristics.

8.2. Time period and frequency for collecting adverse event and serious adverse event information

AE collection: In this study, AEs will be collected from the time the subject signs the informed consent form to the time point specified in the trial flow chart, in which the medical events occurred unrelated to the study intervention from the time of signing the informed consent form to the first medication should be recorded in the CRF as medical history/concomitant diseases, rather than the AE part.

Investigators were not required to actively collect AEs or SAEs following the subject 's safety follow-up period. However, if the investigator learns of any SAE, including death, at any time after a participant leaves the study, and considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly collect a report.

8.3. Methods for collecting adverse events and serious adverse events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and undirected verbal questioning of the subject is the preferred method to inquire about the occurrence of AEs. For example:

"How do you feel?"

"Has your health improved or worsened since the last study visit?"

"Have you taken any new medications since your last study visit? Did you stop taking or change any medication you were taking?"

8.4. Follow-up of adverse events and serious adverse events

Following this initial AE/SAE report, the investigator is required to follow each subject for further information at subsequent visits/contacts. All SAEs, AEs related to the study, or causing the subject to discontinue study treatment should be followed until the event resolves (including return to baseline values), status changes to long-term stabilization, loss to follow-up, death, or the investigator does not consider continued follow-up or other reasonable explanation. The investigator is responsible for performing or arranging for medically indicated or sponsor-requested follow-up visits to elucidate as fully as possible the nature and causality of the AE or SAE.

When reporting follow-up information, the investigator should update the information with the original electronic report form, print the paper report form and re-sign the name and

date. The SAE follow-up report should have the same timelines and procedures as the initial report.

8.5. Recording and assessment of adverse events and serious adverse events

Recording of Adverse Events and Serious Adverse Events

The investigator is responsible for reviewing all documentation (eg, hospital progress notes, laboratory tests, and diagnostic reports) related to the event and recording all relevant information on the AE/SAE in the case report form. The investigator will try to determine the diagnosis of each event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (rather than individual signs/symptoms) was recorded as an AE/SAE. If the diagnosis is unknown, AE names may be temporarily reported as symptoms, signs and abnormal examinations, and each symptom, sign and examination should be recorded separately; when the diagnosis is confirmed later, the records should be updated.

In principle, the investigator should not send copies of the subject 's medical records to Simcere, and in some cases Simcere may request copies of the medical records for some cases, in which case the identification information of all subjects (except subject codes) should be obscured (blackened, etc.) before the copies of the medical records are submitted to Simcere.

During the collection and evaluation of AEs and SAEs, the AE name, start time, stop time or outcome, severity, seriousness, concomitant diseases, concomitant medication, event description, causality assessment, etc. need to be recorded.

Severity of Adverse Events and Serious Adverse Events

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used in this study to evaluate the severity of all adverse events. If there are no AEs defined in NCI-CTCAE, refer to the following rules for severity:

Table 10 Adverse event severity grade not defined in NCI-CTCAE 5.0

Grading	Rule
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic tests only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living (eg, preparing meals, shopping or buying clothes, using the telephone, managing money, etc.).
Grade 3	Severe or clinically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (ability to bathe, dress and undress, eat, go to the toilet, take medications, and not bedridden, etc.).

Grade 4	Life-threatening consequences; urgent medical intervention indicated
Grade 5	Adverse events leading to death

Degree is a category used to assess the intensity of an event, and both adverse events and serious adverse events can be assessed as severe.

Causality Assessment for Adverse Events and Serious Adverse Events

Causality assessment is one of the criteria used in determining regulatory reporting requirements. The investigator is responsible for assessing the relationship between study treatment and the occurrence of each AE/SAE. The investigator judges whether an AE is causally related to the drug and will consult the IB or product information for marketed products and consider the following:

- Is there a temporally reasonable relationship between the onset of the AE and the investigational drug? Is there a time interval between the onset of the AE and the first and last dose?
- Whether the symptoms and signs occurred can be caused by the action mechanism of the drug itself or the action of metabolic components?
- After dose reduction or discontinuation, the symptoms/signs are relieved or improved in the absence of other treatments for AEs?
- Did the symptoms/signs recur or worsen after taking the drug again?
- Can it be explained by the subject 's concomitant diseases, concomitant medication or other reasons?
- Whether similar situations have been reported in domestic and international literatures?

Then, a five-point method (definitely related, probably related, possibly related, unlikely related, definitely unrelated) was used to provide a causality assessment of the relationship between the reported adverse events and the use of the investigational product.

For each AE/SAE, the investigator must document, review, and provide a causality assessment (although information that the investigator may have known was limited in the event of an SAE at some time) and update the causality assessment based on follow-up information.

In this study, SAE reports were classified as "unrelated" in dichotomy if their causality assessment was "possibly unrelated" when further assessing whether they met the criteria for expedited reporting of suspected unexpected serious adverse reactions.

8.6. Regulatory reporting requirements for serious adverse events

After the investigator learns of any SAE, whether or not the SAE is related to the investigational product and listed in the IB, the investigator should report it in accordance with relevant regulatory requirements to meet the legal obligations and ethical responsibilities for the safety of subjects and the safety of clinical studies. The Investigator shall properly maintain written evidence of all reports above to show that each event received has been properly reported.

The sponsor will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, ethics committees (IECs), investigational sites, and investigators, and will inform local and other regulatory authorities of safety information on the investigational product as required and in accordance with sponsor policy. The investigator will review investigator safety reports received from the sponsor describing SUSARs or other specific safety information and then file them with the IB and notify the Ethics Committee.

The sponsor will promptly investigate SAEs with the investigator and take necessary measures to ensure the safety and rights and interests of the subjects.

8.7. Reporting serious adverse events to sponsor

The investigator or designee must complete an expedited SAE report within 24 hours of becoming aware of the subject 's SAE, including as much detail and useful information as possible. Reporting was to be completed within 24 hours even if all information on the SAE was not available at that time. The investigator should update the SAE report within 24 hours of obtaining additional relevant information.

The investigator or designee will fill in the relevant information using the Serious Adverse Event (SAE) Reporting Form, print it on paper and sign the date and name, and scan it by email within 24 hours (i.e. pv@zaiming.com) Sent to Sponsor.

8.8. Pregnancy events

All subjects participating in this study should use a reliable method of contraception from signing the informed consent form to 3 months after the last dose to avoid pregnancy by themselves or the female partner of a male subject. However, if any pregnancy occurs in the subject (or female partner of a male subject) himself/herself (or the female partner of a male subject) after the subject has received at least 1 dose of study drug and up to 3 months after the

last dose, the investigator should examine the safety of the subject and fetus and give appropriate measures as soon as he/she finds it; and the pregnancy information should be recorded on the pregnancy report form and reported to the sponsor within 24 hours of awareness.

All pregnancies should be followed to outcome until full term (generally 6-8 weeks after the expected date of delivery) or premature termination (including spontaneous or elective abortion).

Although pregnancy itself is not considered an AE or SAE, pregnancy complications or elective termination of pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were considered SAEs and were reported as SAEs (both Pregnancy Event Report Form and Serious Adverse Event (SAE) Report Form were to be completed).

In principle, any female subject who became pregnant while participating in this study was to discontinue study drug immediately.

8.9. Adverse events of special interest (AESIs)

During this study, the investigator or designee will use the designated report form to email the subject within 24 hours of becoming aware of an AESI of Trilaciclib that is ⩾Grade 3 (CTCAE 5.0) (i.e. pv@zaiming.com) Sent to Sponsor.

- Injection site reaction/phlebitis/thrombophlebitis
- Acute drug hypersensitivity Reaction
- Pneumonitis/Interstitial Lung Disease
- Hepatotoxicity
- Embolic/Thrombotic Events, Venous

9. Study procedures

9.1. Test flow table I

Table 11 1st line ES-SCLC Patients Study Procedures (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											
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	

	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
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.
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.

	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

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.

9.2. Test flow table II

Table 12 2nd/3rd 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 [f]	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**
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 conditions																	X

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.

	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

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 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).

	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

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.

10. Statistical analysis

10.1. Determination of sample size

The study consists of 2 parts. 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 was not based on statistical calculations, but to support PK evaluation and safety run-in. In addition, assuming a 5.3% occurrence of severe neutropenia (G1T28-02), there is an approximately 28% probability of developing at least one severe neutropenia in 6 patients; if the occurrence of severe neutropenia is 40.6% (G1T28-03), then the probability is 96% to detect at least one 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 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 was 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 was 10% in the Trilaciclib group and 45% in the placebo group, the means of Poisson distributions were 0.105 and 0.598 for the corresponding Trilaciclib and placebo groups, respectively. The stochastic simulation was 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 was 80 subjects (40 per group).

10.2. Analysis set

Full Analysis Set (FAS): All enrolled subjects who received at least one dose of study drug according to the intention-to-treat (ITT) principle. Efficacy analyses will be based on the FAS

set unless otherwise specified. The second part, limited to all randomized subjects, will be analyzed according to the randomized treatment group.

Per-Protocol Analysis Set (PPS): Subjects who had major protocol violations and were judged to have major impact on the results were excluded from the FAS. The PPS set is a subset of the FAS set and the exclusion criteria need to be finalized prior to database lock. The PPS may be used for the analysis of individual endpoints.

Response Evaluable Analysis Set (RES): All subjects who took at least one dose of study drug, had measurable lesion at baseline, and completed at least one post-treatment tumor imaging assessment. This analysis set was used for the analysis of efficacy measures according to RECIST assessment of tumors.

Safety analysis set (SS): All subjects who have received at least one dose of study drug. Safety analyses were based on the SS set by actual treatment received.

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

10.3. Statistical methods

10.3.1. Basic method

Part I

The PK profile will be characterized and safety and tolerability will be evaluated based on Cycle 1 data. In addition, preliminary efficacy (prevention of myelosuppression) data will be summarized.

Part II

It is mainly used to verify the effectiveness of Trilaciclib treatment (prevention of bone marrow suppression). The primary endpoint was DSN in Cycle 1. Unless otherwise specified, efficacy endpoints will be analyzed in the FAS. Some of these endpoints may be analyzed based on the PP. Descriptive statistics for continuous data will include means, medians, standard deviations and ranges, and categorical data will provide counts and percentages. Time-to-event data will be analyzed using the Kaplan-Meier method.

Detailed statistical methods, including sensitivity analyses, handling of missing values, etc, will be presented in the Statistical Analysis Plan (SAP).

10.3.2. Summary of study conduct

Study enrollment, medications, reasons for discontinuation, and reasons for discontinuation will be summarized by treatment group. Major protocol deviations, including those for inclusion and exclusion criteria, will be listed and summarized by treatment group.

10.3.3. Treatment group comparability summary

For demographics (including age, gender, etc.) and baseline characteristics (including baseline conditions, etc.), continuous variables will be summarized using descriptive statistics (mean, standard deviation, median, range, etc.) and categorical variables will be summarized using counts and proportions, as appropriate.

Unless otherwise specified, baseline measurements are defined as the last available valid measurement prior to the first dose.

10.3.4. Primary efficacy endpoint analysis

The primary endpoint was DSN in Cycle 1. For subjects with at least 1 occurrence of severe neutropenia (SN) in Cycle 1, Cycle 1 DSN was defined as the number of days from the date of the first ANC value $< 0.5 \times 10^9$/L 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 was $< 0.5 \times 10^9$/L, and (2) there were 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 was counted as Day 1 of Cycle 2). If the subject did not experience any SN during Cycle 1, Cycle 1 DSN was scored as 0.

Nonparametric analysis of covariance (Nonparametric ANCOVA) will be used to evaluate the efficacy of Cycle 1 DSN. Mean differences between treatment groups, standard errors, and their 95% confidence intervals based on Satterthwaite t tests were also provided.

Detailed definitions, handling of missing values, and detailed analysis methods for Cycle 1 DSNs will be provided in the SAP.

10.3.5. Secondary efficacy endpoint analyses

Key secondary efficacy endpoints

Key secondary efficacy endpoints included SN occurrence, occurrence of red blood cell transfusion (on/after Week 5), occurrence of use of granulocyte colony-stimulating factor (G-CSF), composite endpoint - major hematological adverse events, etc. Descriptive statistics will be used for summarization. Descriptive statistics for continuous data will include mean, median, standard deviation and range. Categorical data will provide counts andpercentages, and the differences between groups and their 95% confidence intervals will be estimated.

Other secondary efficacy endpoints

Other secondary efficacy endpoints included the occurrence of grade 3/4 hematologic toxicities, trough absolute neutrophil count at each 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.

Detailed analysis methods for key secondary efficacy endpoints and other secondary efficacy endpoints will be presented in the SAP.

10.3.6. Safety analysis

Safety analyses will be based on the Safety Analysis Set. Safety evaluations included monitoring of treatment emergent adverse events (TEAEs), physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests (hematology, blood chemistry, and urinalysis) throughout the treatment period.

Descriptive statistics will be used to analyze adverse events, laboratory test indicators, vital signs and ECG, and summarized according to the treatment groups actually received.

Extent of exposure will be summarized as duration of treatment and dose of study drug taken during the treatment period.

According to the vital signs data at baseline and each visit time point, each indicator of vital signs at each visit time point and the change from baseline were statistically summarized.

According to the laboratory test results at baseline and each visit time point, the results of laboratory test items completed at each visit time point and the positive and abnormal changes from before treatment were statistically summarized.

Only treatment-emergent adverse events were counted. A TEAE was defined as an untoward medical occurrence that emerged during treatment or worsened relative to pretreatment. All AEs 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), Preferred Term (PT) and investigational product grouping. List the serious adverse events after medication, adverse

events leading to drug withdrawal, adverse events leading to dropout and drug-related adverse events, and describe the details of each adverse event/adverse reaction in each subject in a separate table, including the type, severity, occurrence and duration, outcome of adverse events as well as their relationship with the investigational drug and the dose of the drug.

Concomitant medications will be reported using summary tables.

10.3.7. 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.

Detailed analysis methods will be given in the SAP. Population pharmacokinetic analysis methods will be presented in an independent population pharmacokinetic analysis plan.

10.3.8. Data analysis time

When the subjects in Part I have completed safety and PK assessments in Cycle 1, an analysis will be performed to characterize the PK profile and evaluate the safety and tolerability based on Cycle 1 data. In addition, preliminary myeloprotective efficacy (prevention of chemotherapy-induced myelosuppression) data will be summarized. Data from 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 randomized subjects in Part II. The sponsor 's necessary personnel will be unblinded, but the investigator, subject, and other personnel will remain blinded. The primary measure of myeloprotective efficacy, duration of severe neutropenia (DSN) in Cycle 1, as well as other applicable secondary or exploratory endpoints, will be assessed 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 of Part II will be performed at the end of the study.

10.3.9. Exploratory analyses

Descriptive statistics will be used to summarize exploratory endpoints, progression-free survival (PFS), overall survival (OS), population pharmacokinetic characteristics, etc. Detailed analysis methods will be presented in the SAP.

The analysis methods for population pharmacokinetics will be presented in a separate SAP analysis plan for population pharmacokinetics.

Exploratory analyses may not be included in the clinical study report based on actual circumstances.

11. Supporting documentation and clinical operations related considerations

11.1. Management of study drug

11.1.1. Dosage form, appearance, packaging, and labeling of study drug

Trilaciclib is supplied as a sterile powder in packaging and labeling information according to local laws and regulations and is labeled for clinical trial use only.

Placebo was formulated as the vehicle for Trilaciclib – 250 mL of 5% dextrose in water or saline (0.9% sodium chloride)

Packaging and labeling information for carboplatin, etoposide, and topotecan are detailed in the package insert.

11.1.2. Receipt and storage of study drug

All study drugs in this study will be supplied uniformly by the sponsor, and the study site will receive and manage the study drugs by a designated person. The actual placebo used was provided by the study site and reimbursed by the sponsor. The site should maintain and manage the study drugs according to the storage conditions provided by the sponsor in strict compliance with relevant regulations in Good Clinical Practice.

All study drug was stored in a secure area until dispensed to subjects and was accessible only to authorized personnel. The study drug manager was required to adequately supervise the storage environment and the associated temperature/humidity logs were maintained as source documents. All study drugs must be used for this study and not diverted.

The investigator should ensure that all study drugs are used in accordance with this protocol.

11.1.3. Drug administration, distribution and recovery

Qualified or experienced study team personnel prepared the study drug administration according to the instructions for study drug (including investigational and non-investigational products) (if applicable) and the drug management manual. Study medication was dispensed at

each visit by qualified personnel. They will dispense the study drug according to the quantity specified in the process each time.

Destruction of Study Drug

To be completed by the sponsor or its authorized unblinded personnel. Ensure that the destruction complies with applicable provisions in applicable environmental regulations, unit policies, etc., and provide relevant destruction procedures. All destruction should be documented.

11.2. Data management

11.2.1. Data collection

According to the study flow chart, at each scheduled visit time point, the investigator will record all significant observations in the original medical records and CRFs, at least including the following:

- Visit Name and Actual Visit Date in Study Flow Chart
- Subject 's general condition and status, including any significant medical findings such as AEs
- Prior/concomitant medications/treatments

Follow-up visits to subjects by telephone or other means will also be documented in the original medical records.

Information from the original medical records must be transcribed to the appropriate section of the CRF in a timely manner.

Changes to the information in the original medical records and other original documents were to be signed and dated by the investigator or his/her designee on the date of change. If necessary, make a brief description of the change adjacent to the change.

11.2.2. Data recording

The important data of each subject in the clinical trial shall be recorded in the CRF. The investigator shall review and agree the completed CRF, and sign the name and date. The Investigator 's signature is to document that the Investigator' s assurance of the completeness, accuracy, and authenticity of the clinical and laboratory data entries in the case report forms. The study was completed using electronic CRFs, which were reviewed and approved/signed by an electronic data capture system (EDC).

Source data refers to clinical findings and observations, laboratory data, and other information contained in source documents. Source documents are original records (and certified copies of original records), including but not limited to hospital medical records,

doctor or office records, doctor or nurse notes, drug distribution and recovery records, automated instrument records, and electrocardiograms. The information recorded in the CRF should be consistent with the source data recorded in the original records.

All CRFs must be completed, modified, and replaced by the investigator or other authorized personnel. If necessary, manual/system-generated Query forms are hosted on the EDC system. The investigator or other authorized personnel must correct the CRF (if applicable) and complete Query 's answers.

If the eCRF needs to be amended after completion, it can be done in 2 ways, but not limited to:

(1) The investigator proactively modifies or answers Query on the EDC system in the EDC tool.

(2) The monitor generates Query for the investigator 's answers.

11.2.3. Database lock

The database will be locked when the following conditions are met.

- All data have been collected and stored;
- All medical codes have been checked and confirmed;
- All data queries have been resolved;
- Database quality control passed;
- Source data verification has been completed;
- Third party data reconciliation has been completed (if any);
- Serious adverse event reconciliation has been completed;
- All Investigator signatures have been obtained;
- Analyzable cases have been defined;
- The Statistical Analysis Plan has been signed.

11.2.4. Data archiving

After completion of the study, if electronic CRFs are used for the study, the subject 's eCRFs will be generated by the EDC system and maintained on a non-rewritable CD for archiving by the sponsor and each institution, respectively, for audit and/or inspection.

The trial data shall be preserved and managed according to GCP requirements, and essential documents for clinical trials shall be preserved until 5 years after the investigational drug is approved for marketing.

11.3. Ethics

11.3.1. Ethics committee

The clinical study protocol and its amendment, Investigator 's Brochure, informed consent form, study-related subject information (such as advertisement for subject recruitment) and other necessary documents should be reviewed by the Ethics Committee.

Ethics Committee approval must be obtained prior to the start of the study and the date the committee met and approved will be indicated in the approval letter to the investigator.

Any amendment to the protocol must be formally approved or filed by the Ethics Committee.

All serious adverse events will be reported to regulatory authorities in accordance with applicable regulatory requirements.

During the course of the study, the investigator should also promptly report to the Ethics Committee any protocol violation that may increase the risk to subjects.

11.3.2. Ethical conduct of the study

The study protocol should be reviewed and approved in written form by the Ethics Committee of the hospital before implementation. The Ethics Committee should be provided with study protocol, protocol amendment, informed consent form and other relevant documents such as recruitment advertisement. This clinical trial must comply with the Declaration of Helsinki, the Good Clinical Practice (GCP) promulgated by the National Medical Products Administration (NMPA) and relevant regulations. Before the start of the trial, approval from the hospital ethics committee must be obtained before the start of the study.

Neither party may unilaterally modify the study protocol without the consent of the study sponsor and the investigator. Only to eliminate an immediate and immediate hazard to subjects, the investigator may modify or deviate from the study protocol prior to obtaining Ethics Committee/Institutional Review Board approval. Meanwhile, the deviations or changes made and reasons thereof, as well as proposed protocol amendments shall be submitted to the Ethics Committee/Institutional Review Board for review as soon as possible. The investigator must explain and document any protocol deviations made.

During the clinical study, any amendment to this study protocol shall be submitted to the Ethics Committee, and other study documents shall be modified accordingly if necessary, and submitted and/or approved in accordance with the requirements of the Ethics Committee. The Ethics Committee should be informed that the trial has ended after the end of the trial.

11.3.3. Subject informed consent

Informed consent form

The informed consent form included all elements as defined by ICH, GCP, and regulatory requirements and complied with the ethical principles set forth in the Declaration of Helsinki. The ICF describes the study drug and study process in detail, and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained prior to the subject performing any study-related procedures.

The ICF should also state that the subject 's personal identity records must be kept confidential, but relevant monitoring, auditing, IEC review and relevant regulatory authorities may refer to the subject' s data.

Informed consent process and documentation

Informed consent begins before an individual agrees to participate in the clinical study and continues throughout the clinical study. The risks and possible benefits of participation will be discussed in detail and fully with the subject or his/her legal representative. Subjects will be asked to read and review the ICF approved by the Ethics Committee. The investigator will explain the clinical study to the subject and answer any questions that the subject may have. Subjects were not allowed to participate in the study until informed consent was obtained. Subjects may withdraw consent at any time during the course of the clinical study. A copy of the informed consent form will be retained by the subject. Even if the enlisted patient refuses to participate in the study, his/her rights will be fully protected and the quality of medical care will not be compromised.

11.3.4. Confidentiality of subject information

Confidentiality of subject information was strictly enforced by the investigator, participating investigators, the sponsor, and their agents. Confidentiality covers biological samples and genetic testing in addition to the subject 's clinical information. Therefore, the study protocol, documentation, data and all other information generated from it will be kept strictly confidential. All relevant study or data information will not be divulged to any unauthorized third party without prior written approval of the Sponsor.

Representatives of other authorized representatives of the sponsor, IECs, or pharmaceutical companies providing study medication by regulatory authorities may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records and subject medication records. The site should allow access to these records.

Subject contact information will be securely maintained at each investigational site and used internally only during the course of the study. At the end of the study, all records will continue to be stored in a secure location for the duration specified by the local IRB and regulations.

11.3.5. Research use of samples, specimens, or data

PROJECTED USE: Samples and data collected under this protocol will be used for drug marketing applications and scientific research related to the drug and will not be used for any unrelated purposes.

Storage: Samples and data will be numbered by the study at the time of storage. Data in the computer will also be password protected. Only researchers have access to these samples and data.

11.3.6. Quality assurance and quality control

To ensure the quality of the trial, the clinical investigation plan was discussed and developed jointly by the sponsor and the investigator before the trial was officially started. Conduct GCP training for relevant study personnel participating in the trial.

Each site must manage the study drug according to the requirements of the study protocol and relevant regulations of the site, including receipt, storage, dispensing, recovery and destruction.

According to GCP guidelines, necessary steps should be taken during the design and conduct of the study to ensure that the data collected are accurate, consistent, complete and credible. All observed results and abnormal findings in clinical trials shall be timely verified and recorded to ensure the reliability of data. The instruments, equipment, reagents and standards used for various inspection items in clinical trials shall have strict quality standards and ensure that they work in normal state.

The investigator entered the information required by the protocol into the eCRF, and the monitor verified whether it was completed completely and accurately, and instructed the site staff to make necessary corrections and additions.

Drug regulatory authorities, Independent Ethics Committees (IECs), monitors and/or auditors of the sponsor may systematically inspect trial-related activities and documents to evaluate whether the trial is conducted according to the requirements of the trial protocol and relevant regulations (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practice [GMP]), and whether the trial data are recorded in a timely, authentic, accurate, and complete manner.

Monitoring

During the study, the monitor designated by the sponsor will regularly contact and visit the investigator, and will check various records (eCRFs and other data of the subject) in the trial as required, provided that the subject 's privacy is protected in accordance with regulatory requirements. The sponsor 's medical monitor will also review the data in the CRF at any time.

All data in the database will be cleaned by the sponsor. Data quality will be ensured by data query and site confirmation.

AUDIT AND INSPECTION

The sponsor or its representative may audit the study site. Audits include, but are not limited to, study drug supply, completeness of documentation required, informed consent process, comparison of eCRFs to source documents. Investigator agrees and participates in audits conducted in a reasonable manner at reasonable times.

Regulatory authorities may inspect the site during or after the trial. The investigator shall fully cooperate in and timely contact and inform the sponsor of the examination conducted in a reasonable manner at a reasonable time.

11.3.7. Preservation and confidentiality of data

To ensure the evaluation and supervision of the clinical study by the CFDA and the sponsor, the investigator should agree to retain all study data, including the original documents of hospitalization for subjects, informed consent form, case report form, and detailed records of drug distribution. Original records and relevant materials will be stored in locked special filing cabinets, and clinical study data will be stored for at least 5 years after the investigational drug is approved for marketing. Non-investigator and unauthorized personnel should not check, and lock the file cabinet in time after use. Original records were electronically stored in a dedicated computer and access was set. All data of this clinical study is proprietary to Simcere Pharmaceutical. Documentation at the site should not be compromised without prior written agreement between the investigator and the sponsor. If the investigator chooses to provide the trial documents to the other party or to move them elsewhere, the sponsor must be informed. Except as required by the NMPA, the Investigator shall not provide the information in any form to any third party without the written consent of the Sponsor.

- Laboratory data information was retrieved as soon as possible after each examination and entered into the eCRF truthfully, completely, and timely;
- Specially-assigned person shall be responsible for entering data into electronic database, and the electronic database system shall set login name and password;

- Only the subject code will be shown in the statistical analysis and will be used as the unique identifier of subject;
- Subject personal information will be kept confidential as required and will not appear in public publications or conference presentations.

11.4. Protocol amendment

During the study, the investigator should obtain the sponsor 's consent and approval for protocol amendment, and the sponsor should designate relevant personnel to revise the protocol.

The amended protocol must be submitted to the Ethics Committee for approval. Before obtaining approval from the Ethics Committee, the investigator remains in compliance with the original study protocol, unless it is intended to avoid immediate hazards to the subject, or the protocol amendment involves only changes in study management (e.g., change in telephone number, etc.).

11.5. Protocol deviations

In the absence of pre-approval and agreement from the sponsor or sponsor 's agent, and in compliance with both EC and local regulations, the investigator will try not to violate the protocol in its execution unless it is necessary to eliminate an immediate hazard to study subjects. When a protocol execution violation is deemed necessary for an individual subject, the investigator must contact the sponsor as soon as possible to obtain sponsor review and to confirm the impact of the violation on the subject and/or the study. Any significant protocol violation that impacts subject eligibility and/or safety must be reviewed and/or approved by the EC and regulatory authorities and, where feasible, implemented prior to execution of the protocol.

11.6. Publication of study results

The study results are the property of the sponsor. If the Investigator intends to publish any data and information related to the Study, the Investigator shall provide Company with the original or full text of all planned publications (posters, invited presentations or guest presentations) at least 30 days prior to submission for publication or other form of publication, and submit or publish with the written consent of the Sponsor.

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13. Appendices

Appendix 1 ECOG scoring table

Attached Table 1 EOCG Scoring Criteria

Score	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work, but unable to carry out work of a heavy or sedentary nature.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Bedridden, unable to carry on any selfcare.
5	Death

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Appendix 2 List of common CYP3A4 inhibitors or inducers

Attached Table 2 List of common CYP3A4 inhibitors or inducers

CYP Enzymes	Strong inhibitors (≥ 5-fold increase in AUC)	Moderate strong inhibitor (5-fold > ≥ 2-fold increase in AUC)	Weak inhibitor (2-fold > ≥ 1.25-fold increase in AUC)
CYP3A4	Boceprevir, cobicistat, danoprevir, ritonavir, elvitegravir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, obitavir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, telithromycin, triamycine, voriconazole, clarithromycin, edarasib, nefazodone, nelfinavir	Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofepatan, verapamil	Chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosalopitant, isometrine, ivacatropium, lobimide, ranitidine, ranolazine, ticagrelor

CYP Enzymes	Strong Inducers (≥ 80% decrease in AUC)	Moderate strong inducer (80% > ≥ 50 decrease in AUC)	Weak inducer (20% ≤ AUC decreased < 50%)
CYP3A4	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin sodium, rifampin, St. John 's Wort	Bosentan, efavirenz, etravirine, phenobarbital, primidone	Armodafinil, modafinil, rutinamide

Appendix 3 Pharmacokinetic blood sampling schedule

PK blood samples will be collected at the following time points during Cycle 1 of Part I of this study.

Attached Table 3 Blood Collection Schedule -1: Pharmacokinetic Blood Collection Schedule for Trilaciclib (Chemotherapy regimen is carboplatin combined with etoposide)

Date	**D1**									**D2**
Time since end of dosing	**Prior to start of dosing**	**Immediate end of installation (EOI)**	**0.5h**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h (prior to 2nd dose) ***
	Within 0.5h	**± 2 min**	**± 2 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 10 min**	**± 30 min (within 0.5 h before 2nd dose) ***
PK blood sampling	√	√	√	√	√	√	√	√	√	√
Date	**D3**									**D4**
Time since end of dosing	Prior to start of dosing	Immediate end of installation (EOI)	0.5h	1h	2h	4h	6h	8h	12h	24h
	Within 0.5h	± 2 min	± 2 min	± 5 min	± 5 min	± 5 min	± 5 min	± 5 min	± 10 min	± 30 min

PK blood sampling	√	√	√	√	√	√	√	√	√	√

Attached Table 4 Blood Sampling Schedule - 2: Pharmacokinetic Blood Sampling Schedule for Trilaciclib (Topotecan as Chemotherapy Regimen)

Date	**D1**									**D2**	**D3**	**D4**
Time since end of dosing	**Prior to start of dosing**	**Immediate end of installation (EOI)**	**0.5h**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24 hours (before start of 2nd dose) ***	**Before start of 3rd dose**	**Before start of 4th dose**
	Within 0.5h	**± 2 min**	**± 2 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 10 min**	**± 30 min (within 0.5 h before 2nd dose) ***	**Within 0.5h**	**Within 0.5h**
PK blood sampling	√	√	√	√	√	√	√	√	√	√	√	√
Date	**D5**									**D6**	**NA**	**NA**

Time since end of dosing	**Prior to start of dosing**	**Immediate end of installation (EOI)**	**0.5h**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**	**NA**	**NA**
	Within 0.5h	**± 2 min**	**± 2 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 5 min**	**± 10 min**	**± 30 min**	**NA**	**NA**
PK blood sampling	√	√	√	√	√	√	√	√	√	√	NA	NA

*: The blood sampling time on D2 is required to be 24h ± 30 min after the end of D1 administration, and D2 administration is required to be performed within 0.5h after blood sampling.

In Cycle 1 of Part II of this study, PK blood sample collection is planned to be performed at the following time points, and the actual blood collection points could be adjusted according to the pharmacokinetic study results in Part I.

Attached Table 5 Blood Collection Schedule - 3: Trilaciclib Pharmacokinetic Blood Collection Schedule

Date	**D1**			**D2**
Time since end of dosing	**Immediate end of installation (EOI)**	**0.5h**	**5h**	**Before 2nd dose**
	± 5 min	**± 10 min**	**± 1h**	**Within 1 h prior to 2nd dose**
PK blood sampling	√	√	√	√