Clinical Study Protocol

Management Strategy of 1L Lorlatinib With Hyperlipidemia in Stage IIIB-IV ALK Positive NSCLC: A Multi-center Prospective Study in China

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STUDY SYNOPSIS

Protocol Title: *Management strategy of 1L Lorlatinib with Hyperlipidemia in Stage IIIB-IV ALK positive NSCLC: A multi-center prospective study in China*

Study Sponsor(s):	**Compound:**
Prof. Zhang Li	Lorlatinib; Statins: Rosuvastatin, Simvastatin and Pitavastatin; Ezetimibe; Evolocumab.

Background and Rationale

ALK-positive non-small cell lung cancer (NSCLC) is a molecular subtype caused by ALK gene rearrangement, accounting for approximately 3-7% of NSCLC cases[1,2]. Patients with this subtype are typically younger, have a minimal smoking history, and exhibit unique clinical and biological characteristics. In recent years, with the continuous advancement of molecular targeted therapies, ALK tyrosine kinase inhibitors (ALK-TKIs) have significantly improved progression-free survival (PFS) and overall survival (OS) in patients. The first-generation ALK-TKI, crizotinib, notably extended PFS in ALK-positive NSCLC patients[3]. Subsequent development of second-generation TKIs, such as alectinib and brigatinib, further enhanced efficacy, particularly in controlling central nervous system (CNS) lesions[4,5]. However, despite the significant efficacy of second-generation TKIs, most patients eventually experience disease progression due to acquired resistance, posing new challenges for the treatment of ALK-positive NSCLC.

Lorlatinib, a third-generation ALK-TKI, is designed to cross the blood-brain barrier and demonstrates potent activity against multiple ALK resistance mutations, including G1202R[6,7]. In CROWN study, lorlatinib showed remarkable efficacy as a first-line treatment, with both progression-free survival (PFS) and intracranial response rates significantly superior to those of crizotinib[8]. However, treatment with lorlatinib is associated with certain adverse events, among which lipid abnormalities (including hypercholesterolemia and hypertriglyceridemia) are among the most common[8]. Notably, recent efficacy data show that the median PFS with lorlatinib remains unreached after five years of follow-up, with no difference in the risk of cardiovascular events compared to the crizotinib group[8]. As survival improves, the long-term management of patients becomes increasingly critical, necessitating effective management strategies to optimize treatment outcomes.

Current management strategies for drug-induced lipid abnormalities primarily include lifestyle interventions (such as dietary modifications and exercise) and pharmacological treatments. Common lipid-lowering agents include statins (e.g., rosuvastatin, pitavastatin, simvastatin), ezetimibe, and PCSK9 inhibitors (e.g., evolocumab). Statins, which inhibit HMG-CoA reductase to reduce cholesterol synthesis, are the first-line treatment in clinical practice[9].

Ezetimibe, which inhibits cholesterol absorption, can be used in combination with statins to further lower LDL-C levels[10]. PCSK9 inhibitors enhance the recycling of LDL receptors, resulting in significant reductions in LDL-C[11]. Although these agents are widely used, their application in managing lipid abnormalities induced by targeted therapies, such as lorlatinib, requires further investigation. This study aims to evaluate the efficacy and safety of various intervention strategies for managing lorlatinib-associated lipid abnormalities, providing more targeted guidance for clinical practice.	
Protocol Number, if available: <TBD>	**Phase:** Prospective study

Study Design

This study is designed to investigate the efficacy and safety of different lipid-lowering management strategies in ALK-positive NSCLC patients who develop hyperlipidemia during lorlatinib treatment. By exploring these strategies, the study aims to provide evidence-based recommendations for optimizing the long-term management of lorlatinib-associated hyperlipidemia in clinical practice.

Methods

Patient treatment

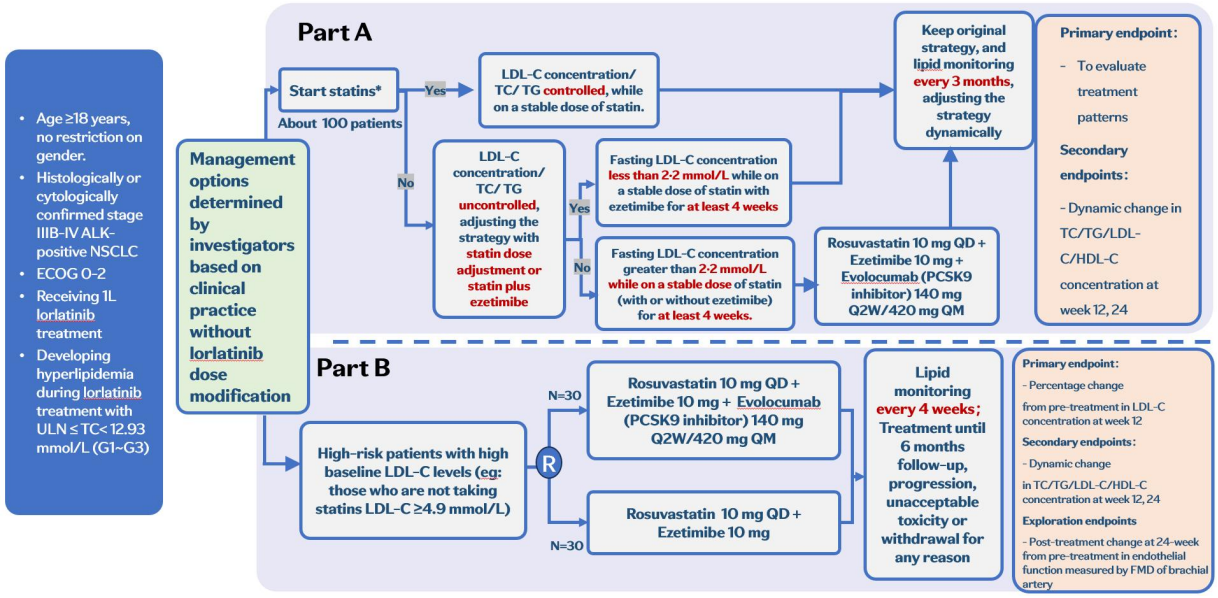
We plan to enrol about 160 stage IIIB-IV ALK-rearranged NSCLC patients treated with 1L lorlatinib.

Part A: In real-world settings, about 100 patients with Grade 1-3 TC elevation (ULN ⩽ TC<12.93mmol/L) will receive hyperlipidemia management following the standard guideline, starting with statins and monitoring lipid level after 4 weeks until under controlling.

Part B: 60 patients with high-risk CVD will be divided into two subgroups:

- **Arm 1:** Patients will be randomly assigned to receive an intensive combination therapy of Rosuvastatin, Ezetimibe, and Evolocumab.
- **Arm 2:** Patients will be randomly assigned to receive Rosuvastatin and Ezetimibe.

This stratified approach will allow the study to assess the differential efficacy and safety of lipid-lowering interventions tailored to the severity of hyperlipidemia during lorlatinib treatment. Patients will undergo a CT scan after 4 weeks (±1 week) from the starting of induction therapy lorlatinib to determine the treatment response that will be assessed by the investigator using RECIST v1.1. All patients signed an informed consent prior to enrolment. Data will not be collected once patient withdrawal from this study.



Statins: Statins (room temperature) are fundamental in lipid management, primarily used to lower low-density lipoprotein cholesterol (LDL-C).

Medication	Starting Dose	Maximum Dose
Rosuvastatin	5-10 mg/day	40 mg/day
Simvastatin	10-20 mg/day	40 mg/day
Pitavastatin	1-2 mg/day	4 mg/day

Ezetimibe: A Cholesterol Absorption Inhibitor. Ezetimibe (room temperature) inhibits cholesterol absorption and can be combined with statins to further reduce LDL-C levels.

Medication	Recommended Dose
Ezetimibe	10 mg/day

PCSK9 Inhibitors: For Severe Hypercholesterolemia

PCSK9 inhibitors are used for severe hypercholesterolemia or when statins and ezetimibe fail to achieve target LDL-C levels.

Medication	Recommended Dose	Usage Instructions
Evolocumab (Store refrigerated at 2°C–8°C in original carton. Do not freeze/shake. Single-use pens may be kept at room temperature (max 30°C) for up to 48 hours)	140 mg every 2 weeks; 420 mg per month	Subcutaneous injection

Primary Objectives

Part A: To evaluate treatment patterns on hyperlipidemia management in stage IIIB-IV ALK+ NSCLC patients with lorlatinib.

Part B: To evaluate the percentage reduction in LDL-C levels after 12 weeks of different lipid-lowering interventions in stage IIIB-IV ALK+ NSCLC patients with lorlatinib with hyperlipidemia.

Secondary Objectives

Dynamic change in TC/TG/LDL-C/HDL-C concentration at week 12, 24

Exploratory Objectives

Endothelial Function Changes: Assess changes in endothelial function from baseline to within 24 weeks of treatment, measured by brachial artery flow-mediated dilation (FMD).

Study Population

Patients with ALK positive stage IIIB to IV Non-small Cell Lung Cancer treated with 1L lorlatinib.

<table>
<tr><td>Number of Subjects
160 patients</td><td>Number of Sites:
8 sites in China</td></tr>
<tr><td>Dose Level(s):
Lorlatinib, 100mg, QD;
Statins: Rosuvastatin 5-10 mg QD; Simvastatin 10-20 mg QD; Pitavastatin 1-2 mg QD; treatment based on clinical practice;
Ezetimibe 10 mg QD;
Evolocumab 140 mg Q2W/420 mg QM.</td><td>Route of Administration:
Lorlatinib, oral;
Statins: Rosuvastatin, Simvastatin and Pitavastatin; oral;
Ezetimibe, oral;
Evolocumab, subcutaneous Injection.</td></tr>
<tr><td>Duration of Treatment
6 months</td><td>Period of Evaluation
6 months</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion (Part A + B)
• Age ≥18 years, no restriction on gender.
• Histologically or cytologically confirmed stage IIIB-IV ALK-positive non-small cell lung cancer (NSCLC).
• ECOG performance status (PS) score of 0-2.
• Developing hyperlipidemia during 1L lorlatinib treatment with ULN ≤ TC< 12.93 mmol/L (G1~G3)
• The patient or their legal representative has signed the informed consent form.
Part B Criteria for Inclusion
• Defined as patients with 1 major ASCVD event, or baseline LDL-C ⩾ 4.9 mmol/L ± high-risk conditions.
Major ASCVD Events:
1) Recent acute coronary syndrome (ACS) within the past year
2) History of myocardial infarction (excluding recent ACS)
3) History of ischemic stroke
4) Symptomatic peripheral arterial disease (PAD), including prior revascularization or amputation
High-Risk Conditions (prefer considered):
1) Recurrent major ASCVD event despite LDL-C ⩽ 1.8 mmol/L
2) Premature coronary heart disease (male <55 years; female <65 years)
3) Familial hypercholesterolemia</td></tr>
</table>

4) History of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)

5) Diabetes mellitus

6) Hypertension

7) Stage 3–4 chronic kidney disease (CKD)

8) Active smoking

Main Criteria for Exclusion

- Mixed squamous cell carcinoma, large cell carcinoma, small cell lung cancer.
- Prior treatment with any systemic anti-cancer therapy for NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug.
- Diagnosed with hereditary hypercholesterolemia (e.g., familial hypercholesterolemia, only for Part A) or other clearly defined secondary dyslipidemia (e.g., hypothyroidism, uncontrolled diabetes, nephrotic syndrome).
- Known allergy or history of severe adverse reactions to the study drugs (including lorlatinib, statins, ezetimibe, or evolocumab).
- Presence of other severe diseases that could affect study compliance or outcome evaluation, including advanced renal failure (eGFR <30 mL/min/1.73 m²), or severe hepatic impairment (Child-Pugh class C).
- Pregnant or lactating women, or women and men of childbearing potential unwilling to use effective contraception during the study.
- Currently participating in another interventional clinical study that may interfere with the treatment under investigation. Patients expected to be unable to complete study follow-up or the first tumor efficacy evaluation. Patients with mental or psychological disorders that impair their ability to provide informed consent or adhere to study requirements, including treatment and follow-up.

Main Criteria for Evaluation and Analyses

Primary endpoint: (Part A) Evaluate treatment patterns on hyperlipidemia management; (Part B) Percentage change from pre-treatment in LDL-C concentration at week 12

Secondary endpoints: Dynamic change in TC/TG/LDL-C/HDL-C concentration at week 12, 24

Exploratory Endpoints: Post-treatment change at 24-week from baseline in endothelial function measured by FMD of brachial artery

Patient Follow-up and Data Collection

1. Baseline Assessment

- Demographics and Medical History: Collect patient demographic data, medical history, and medication history.
- Lipid Profile and Cardiovascular Risk: Record baseline lipid levels, including total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG), and assess cardiovascular risk.
- Tumor Baseline Evaluation: Perform a comprehensive tumor evaluation, including imaging studies.

2. Follow-up Time Points

Part A

- Lipid Monitoring: Monitor lipid levels at Week 4, Week 8, Week 20 and Week 24 of treatment as available.

Part B

- Lipid Monitoring: Monitor lipid levels at Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 of treatment.
- Exploratory Indicators: Conduct additional assessments of exploratory indicators (e.g., flow-mediated dilation [FMD]) at Week 24.

Randomization and Blinding

1. **Randomization (for Part B)**
    - **Patient Allocation:** 60 Patients with high baseline LDL-C levels will be randomly assigned in a 1:1 ratio to either Arm 1 or Arm 2.
    - **Method:** Randomization will be performed using a computer-generated random number table and implemented by an independent third party to ensure objectivity.
2. **Blinding**
    - **Study Design:** This is an open-label study, where both patients and investigators are aware of group assignments.
    - **Blinded Data Analysis:** To minimize bias, blinded data processing will be employed during the statistical analysis phase.

Sample Size Justification

- Part A: Given the exploratory nature of this real-world study and the inherent variability in real-world data, a pragmatic sample size of approximately 100 patients was deemed sufficient to provide preliminary insights into treatment patterns. While formal power calculations were not performed due to the observational design, this sample size aligns with similar RWE studies in NSCLC and allows for meaningful descriptive analyses. Further details on statistical considerations are provided in the Statistical

Analysis Plan.

- Part B: This study aims to compare the percentage change in LDL-C levels from pre-treatment to Week 12 between the treatment and control groups using a 2×2 repeated measures design. Assuming a 20.0% difference in LDL-C percentage change between the two groups (arm 1 and arm 2) at Week 12, with a standard deviation (σ) of 25% for the percentage change at both pre-treatment and Week 12, and setting the significance level (α) at 0.05 and power at 0.8, the required sample size is 26 patients per group. Considering a 10% dropout rate, the final enrollment target is 30 patients per group to ensure sufficient statistical power for detecting meaningful differences. Further details on statistical considerations are provided in the Statistical Analysis Plan.

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1. Introduction

ALK-positive non-small cell lung cancer (NSCLC) is a molecular subtype caused by ALK gene rearrangement, accounting for approximately 3-7% of NSCLC cases[1,2]. Patients with this subtype are typically younger, have a minimal smoking history, and exhibit unique clinical and biological characteristics. In recent years, with the continuous advancement of molecular targeted therapies, ALK tyrosine kinase inhibitors (ALK-TKIs) have significantly improved progression-free survival (PFS) and overall survival (OS) in patients. The first-generation ALK-TKI, crizotinib, notably extended PFS in ALK-positive NSCLC patients[3]. Subsequent development of second-generation TKIs, such as alectinib and brigatinib, further enhanced efficacy, particularly in controlling central nervous system (CNS) lesions[4,5]. However, despite the significant efficacy of second-generation TKIs, most patients eventually experience disease progression due to acquired resistance, posing new challenges for the treatment of ALK-positive NSCLC.

Lorlatinib, a third-generation ALK-TKI, is designed to cross the blood-brain barrier and demonstrates potent activity against multiple ALK resistance mutations, including G1202R[6,7]. In CROWN study, lorlatinib showed remarkable efficacy as a first-line treatment, with both progression-free survival (PFS) and intracranial response rates significantly superior to those of crizotinib[8]. Lorlatinib was designed to cross the blood–brain barrier in order to achieve high exposures in the central nervous system (CNS).[9,10] In phase 1 and 2 studies, lorlatinib had potent antitumor activity after the failure of previous ALK TKIs (first-generation, second-generation, or both).[10,11] In particular, lorlatinib had marked intracranial activity in previously treated patients with baseline CNS disease, including leptomeningeal disease.[11] In an ongoing China only phase 2 study, lorlatinib exhibited highly consistent antitumor activity, intracranial efficacy and safety profile as global phase 2 study in patients with progression on ALK TKIs,[12] reconfirming superior efficacy of lorlatinib in combating ALK resistance. After a median follow-up of five years (60.2 months), the CROWN study demonstrated unprecedented efficacy of lorlatinib compared to first-generation crizotinib. The median progression-free survival (PFS) with lorlatinib had not yet been reached, with a 81% reduction in the risk of disease progression or death (hazard ratio [HR] = 0.19). The five-year PFS rate in the lorlatinib group was as high as 60%[8]. This represents the longest PFS benefit ever reported for a targeted monotherapy in advanced non-small cell lung cancer (NSCLC) and even in advanced solid tumors, establishing a new benchmark in targeted therapy for lung cancer. Additionally, data presented at the 2024 ESMO conference showed that the benefit observed in the overall patient population was highly consistent in the Asian subgroup (HR = 0.22). In the CROWN study, lorlatinib reduced the risk of intracranial (IC) disease progression by 94%, with no intracranial progression occurring in the lorlatinib group for 3-5 years, suggesting that lorlatinib effectively delays intracranial progression. Among patients without baseline brain metastases, the proportion of patients in the lorlatinib group without intracranial progression reached 96%, with a HR for time to intracranial progression of 0.05 (95% CI, 0.02-0.13), further demonstrating that lorlatinib is more effective than crizotinib in preventing brain metastasis. Moreover, lorlatinib showed a therapeutic advantage in patients who were previously difficult to treat with ALK TKIs, such as those with EML4-ALK V3 variants or TP53 mutations[8]. In the lorlatinib group, the median PFS for patients with the EML4-ALK V1 variant was 64.3 months, while the median PFS for patients with the EML4-ALK V3 variant was 60.0 months. In patients with TP53 mutations, the median PFS was 51.6 months,

compared to the median PFS that had not yet been reached in patients without TP53 mutations[8]. These efficacy results were superior to those observed with crizotinib and were highly consistent with the overall population benefit.

Most adverse events (AEs) can be effectively managed through dose adjustments, treatment interruptions, or concomitant therapies. In the CROWN study, the incidence of grade 3/4 treatment-related adverse events (AEs) was 77% in the lorlatinib group and 57% in the crizotinib group[8]. The most common AEs associated with lorlatinib included hypertriglyceridemia, hypercholesterolemia, weight gain, and hypertension. Only 5% of patients in the lorlatinib group permanently discontinued treatment due to treatment-related AEs, indicating that lorlatinib-associated AEs are manageable and controllable[8]. Notably, recent efficacy data show that the median PFS with lorlatinib remains unreached after five years of follow-up, with no difference in the risk of cardiovascular events compared to the crizotinib group[8]. As survival improves, the long-term management of patients becomes increasingly critical, necessitating effective management strategies to optimize treatment outcomes.

Current management strategies for drug-induced lipid abnormalities primarily include lifestyle interventions (such as dietary modifications and exercise) and pharmacological treatments. Common lipid-lowering agents include statins (e.g., rosuvastatin, pitavastatin, simvastatin), ezetimibe, and PCSK9 inhibitors (e.g., evolocumab). Statins, which inhibit HMG-CoA reductase to reduce cholesterol synthesis, are the first-line treatment in clinical practice[13]. Ezetimibe, which inhibits cholesterol absorption, can be used in combination with statins to further lower LDL-C levels[14]. PCSK9 inhibitors enhance the recycling of LDL receptors, resulting in significant reductions in LDL-C[15]. Although these agents are widely used, their application in managing lipid abnormalities induced by targeted therapies, such as lorlatinib, requires further investigation. This study aims to evaluate the efficacy and safety of various intervention strategies for managing lorlatinib-associated lipid abnormalities, providing more targeted guidance for clinical practice.

2. STUDY OBJECTIVES

2.1. Objectives

Primary Objective:

- **Part A:** To characterize the real-world treatment patterns for hyperlipidemia management in patients with stage IIIB–IV ALK-positive non-small cell lung cancer (NSCLC) receiving lorlatinib.
- **Part B:** To assess the percentage reduction in low-density lipoprotein cholesterol (LDL-C) levels at Week 12 following different lipid-lowering interventions in stage IIIB–IV ALK-positive NSCLC patients treated with lorlatinib who develop hyperlipidemia.

Secondary Objectives:

To evaluate the dynamic changes in total cholesterol (TC), triglycerides (TG), LDL-C, and high-density lipoprotein cholesterol (HDL-C) at Weeks 12 and 24.

Exploratory Objectives:

To assess changes in endothelial function from baseline to within 24 weeks of treatment, as measured by brachial artery flow-mediated dilation (FMD).

2.2. Endpoints

Primary Endpoint:

- **Part A:** Description and categorization of hyperlipidemia management strategies in stage IIIB–IV ALK-positive NSCLC patients receiving lorlatinib.
- **Part B:** Mean percentage change from baseline in LDL-C levels at Week 12 following different lipid-lowering interventions.

Secondary Endpoints:

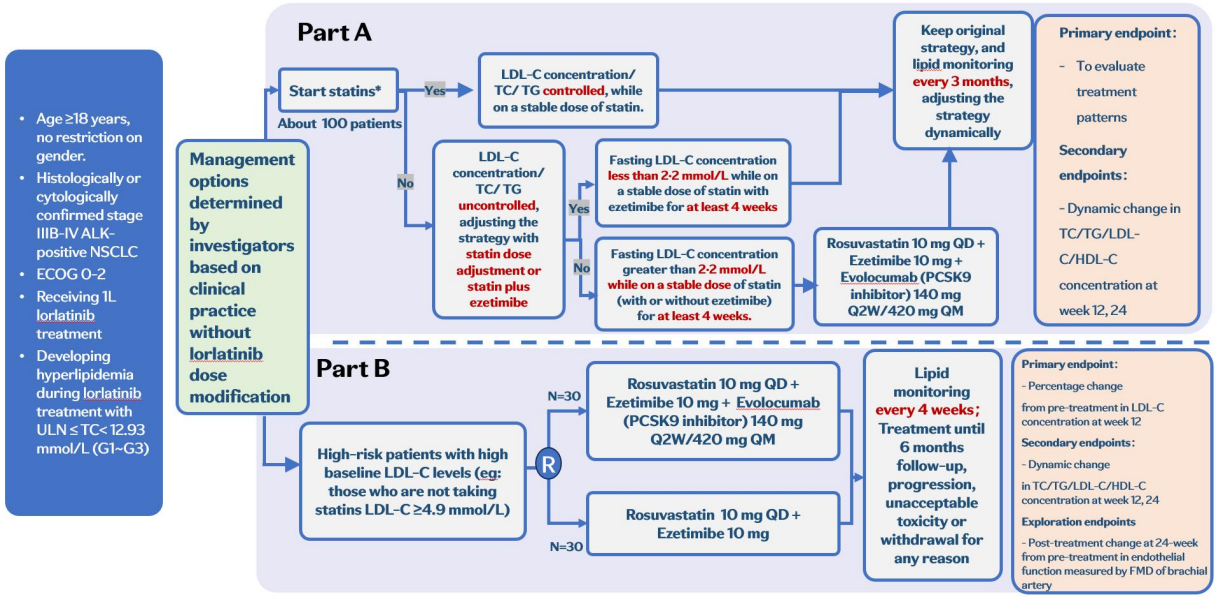
Mean and median changes from baseline in TC, TG, LDL-C, and HDL-C at Weeks 12 and 24.

Exploratory Endpoints:

Change in brachial artery flow-mediated dilation (FMD) from baseline to within 24 weeks of treatment.

3.1 Study design

Figure 1. Study Design



Study Type:

Part A: Observational, prospective, real-world cohort study

Part B: Prospective, randomized, controlled trial (RCT)

Study Period: Estimated duration: 6 months

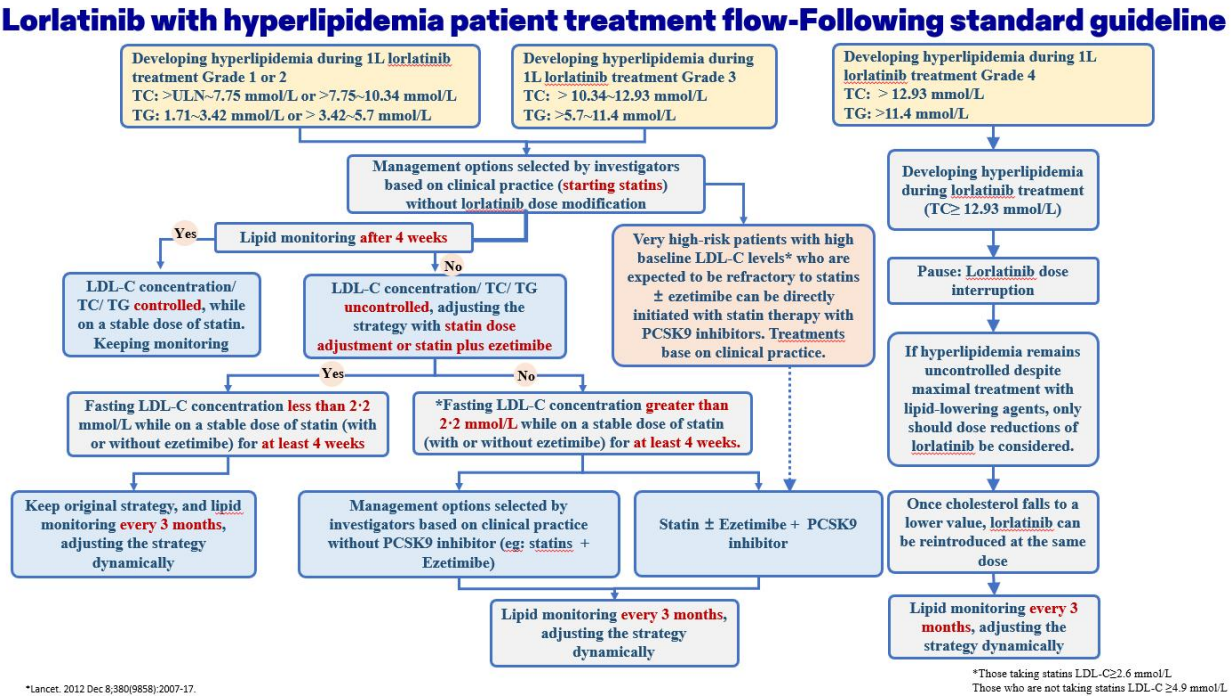
Study Sites: Multicenter (8 sites)

Estimated Sample Size: ~100 patients in Part A, and 60 patients in Part B (30 per group)

Study Phases:

- **Part A:**
    - Baseline assessment and documentation of lorlatinib-associated hyperlipidemia
    - Treatment strategy documentation
    - Baseline, 4-week, 8-week, 20-week and 24-week follow-up of lipid parameters

Part A is a real-world study involving approximately 100 patients. Given the exploratory nature of this real-world study and the inherent variability in real-world data, a pragmatic sample size of approximately 100 patients was deemed sufficient to provide preliminary insights into treatment patterns. While formal power calculations were not performed due to the observational design, this sample size aligns with similar RWE studies in NSCLC and allows for meaningful descriptive analyses. Further details on statistical considerations are provided in the Statistical Analysis Plan. The study aims to document the lipid management strategies employed in response to lipid elevation caused by first-line lorlatinib treatment. In accordance with existing lipid management guidelines, statins are prioritized for lipid control following the onset of elevated lipid levels. If lipid levels remain high after 4 weeks, adjustments to the statin dosage or the addition of ezetimibe will be considered for further lipid control. Lipid levels will be re-evaluated after an additional 4 weeks. If lipid levels are still not optimally controlled, the initiation of a PCSK9 inhibitor in combination with the current regimen will be recommended. However, if lipid levels are well-controlled during the monitoring period, the frequency of lipid monitoring can be reduced to once every three months. (Figure 2. Standard guideline)



- **Part B:**
  - Randomization to different lipid-lowering intervention arms
  - LDL-C measured at baseline and Week 12
  - Comparison of efficacy between intervention arms

Part A is a randomized controlled trial (RCT) involving a total of 60 patients, with 30 patients in each group. The study aims to investigate the effect of different lipid management strategies on the reduction of LDL-C levels in patients who experience lipid elevation due to first-line lorlatinib treatment and have high-risk factors. Patients with high-risk factors will be randomly assigned to one of two groups: **Intervention Group:** Patients in this group will receive intensive lipid-lowering therapy, including rosuvastatin, ezetimibe, and evolocumab. **Control Group:** Patients in this group will receive standard lipid-lowering therapy, consisting of rosuvastatin and ezetimibe. The primary objective is to compare the reduction in LDL-C levels after 12 weeks of management between the two groups. Lipid levels will be monitored every 4 weeks during the follow-up period, which will continue for a total of 6 months. This study aims to compare the percentage change in LDL-C levels from pre-treatment to Week 12 between the treatment and control groups using a 2×2 repeated measures design. Assuming a 20.0% difference in LDL-C percentage change between the two groups at Week 12, with a standard deviation (σ) of 25% for the percentage change at both pre-treatment and Week 12, and setting the significance level (α) at 0.05 and power at 0.8, the required sample size is 26 patients per group. Considering a 10% dropout rate, the final enrollment target is 30 patients per group to ensure sufficient statistical power for detecting meaningful differences.

The study duration will be approximately 4 years. The enrollment period is planned to be about 24 months (from first site initiation, until the planned number of patients reached). The follow-up period per patient is up to 7 months

from the time patients who received lorlatinib enrolled in this study. The study is expected to be closed in about Dec 2029.

(Effectiveness assessments were performed throughout the treatment period and at the end-of-study visit. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was used for tumor assessment at screening,at baseline, 4 weeks after lorlatinib treatment and then every 8-12 weeks. For patients with brain metastases, RANO-BM criteria was used for intracranial lesions. Gadolinum-enhanced brain MRI is recommended at baseline and 4 weeeks after lorlatinib treatment.)

All patients (regardless of the reason for discontinuation from study treatment) were to be followed for subsequent anti-cancer systemic therapies and survival status approximately every 6 months from the post-treatment follow-up visit. Patients with no evidence of disease progression at the time of permanent treatment discontinuation were to be followed until disease progression; for these patients, repeat tumor assessments were suggested to occur approximately every 8-12 weeks from the date of the CT/MRI at the end-of-study treatment. Subjects should be instructed to take their medication at approximately the same time every day. Throughout the study, there was no fixed schedule of visits and hyperlipidemia assessments, and effectiveness assessments will follow local clinical routine.

Data Source/Data Collection:

Data will be collected from approximately 8 hospitals. The data is sourced from the hospital information system (HIS)/electronic medical record (EMR)/laboratory information system (LIS)/ picture archiving and communication system (PACS), and genetic testing report data. All data collection will be done using data management platform. All data are based on medical records or genetic testing reports if available. The investigators at the sites are responsible for ensuring that the required data is collected and entered the data management platform.

For each patient, the attending physician will document the clinical information during the initial visit, follow-up visits, and the final visit. The attending physician will document the baseline data (demographic and baseline disease characteristics) from medical records or through an interview at an initial visit. When patients who received lorlatinib enrolled in this study, follow-up visits are performed by investigator to collect study-related data, including data on effectiveness, tumor status, and other study required variables. A final data collection will be performed at death, withdrawal of consent, loss to follow-up, or the end of the study which is the earliest occurrence. There is no fixed visit schedule; visits will follow local routine clinical practice. Data will be collected until the 60th month after patient enrolled in this study (last follow-up time) or the death of patients due to any cause, loss to follow-up or withdrawal from the study which is the earliest occurrence.

Data type:

The clinical data collected for this study include, but is not limited to:

Collect patients' baseline demographic information (including age at diagnosis, gender, height, weight, physical examination, smoking status), ECOG score, past history, baseline disease characteristics (disease stage, molecular

typing, pathological diagnosis), laboratory test results (blood routine, urine routine, blood biochemistry, coagulation function tests, electrocardiogram, echocardiography, vital signs), ALK genetic testing methods and results, test specimen types, imaging tests (tumor assessment[size, number, and location], medication treatment, adverse events, post-resistance gene testing, dose modification regimens, reasons for lorlatinib dose modification, interruption or discontinuation, PRO (if data is available in clinical practice) and survival status.

Collection and recording of SAEs and AEs on hyperlipidemia will commence once the study participant has provided informed consent and terminate till 28 (and no more than 35) days after administration of the last dose of lorlatinib. After this period, only lorlatinib-related SAEs must be reported to the Pfizer. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). All patients will be periodically contacted for survival and safety information unless the patient requests to be withdrawn from the study. Survival status is also encouraged to be confirmed through a telephone follow-up by the investigator or designee at the end of the study or withdrawal from the study.

3.2 Safety Plan

The overall safety profile and toleration of lorlatinib and locally therapy will be based on AEs and laboratory abnormalities with regard to frequency, severity (in accordance with CTCAE v5.0), timing and relationship with study drug and treatment mode. Throughout the study, all patients treated with lorlatinib are followed for safety to assess the safety of lorlatinib, including AEs leading to dose modification, interruption or discontinuation of lorlatinib and other reasons for dose modification, interruption or discontinuation of lorlatinib in the medical records.

4. SUBJECT SELECTION

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Diagnosis:

   a. Study Population: Patients with histologically or cytologically confirmed diagnosis of locally advanced [(Stage IIIB/C not amenable for multimodality treatment) or metastatic (Stage IV) by American Joint Committee on Cancer (AJCC) v 7.0] ALK-positive NSCLC where ALK status is determined by the Ventana ALK (D5F3) Companion Diagnostic (CDx) IHC test performed on the Ventana ULTRA or XT Platforms, FISH, PCR, or next generation sequencing (NGS), or circulating tumor DNA (ctDNA).

   b. Tumor Requirements: At least 1 measurable target lesion per RECIST v. 1.1 that has not been previously irradiated. Brain metastases are allowed.

2. No prior systemic treatment for advanced (Stage IIIB/C not amenable for multimodality treatment) or metastatic (Stage IV) disease.

3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, 2.

4. Age ⩾18 years.

5. Developing hyperlipidemia during 1L lorlatinib treatment with ULN ⩽ TC< 12.93 mmol/L (G1~G3)

6. Life expectancy at least 6 months.

7. Serum pregnancy test (for females of childbearing potential) negative at screening. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause (which may be confirmed with a serum follicle-stimulating hormone [FSH] level confirming the postmenopausal state if appropriate);

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have medically confirmed ovarian failure.

All other female patients (including female patients with tubal ligations) are of childbearing potential.

8. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Part B Criteria for Inclusion

Defined as patients with 1 major ASCVD event, or baseline LDL-C ⩾ 4.9 mmol/L ± high-risk conditions.

Major ASCVD Events:

1) Recent acute coronary syndrome (ACS) within the past year

2) History of myocardial infarction (excluding recent ACS)

3) History of ischemic stroke

4) Symptomatic peripheral arterial disease (PAD), including prior revascularization or amputation

High-Risk Conditions (prefer considered):

1) Recurrent major ASCVD event despite LDL-C ⩽ 1.8 mmol/L

2) Premature coronary heart disease (male <55 years; female <65 years)

3) Familial hypercholesterolemia

4) History of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)

5) Diabetes mellitus

6) Hypertension

7) Stage 3–4 chronic kidney disease (CKD)

8) Active smoking

4.2 Exclusion Criteria

Subjects presenting with any of the following characteristics/conditions will not be included in this clinical study:

1. Major surgery within 4 weeks prior to randomization. Minor surgical procedures (e.g., port insertion) are not excluded, but sufficient time should have passed for adequate wound healing.

2. Radiation therapy within 2 weeks prior to enrollment, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within 4 weeks prior to randomization or palliative radiation therapy outside of the CNS within 48 hours prior to randomization will also not be included in the study.

3. Gastrointestinal abnormalities, including inability to take oral medication; requirement for intravenous alimentation; prior surgical procedures affecting absorption including total gastric resection or lap band; active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease; treatment for active peptic ulcer disease in the past 6 months; malabsorption syndromes.

4. Known prior or suspected severe hypersensitivity to study drugs or any component in their formulations.

5. History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.

6. Evidence of active malignancy (other than NSCLC, non-melanoma skin cancer, or localized prostate cancer or any in situ cancer which does not currently require treatment) within the last 3 years prior to randomization.

7. Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug fall into any of the above categories) within 12 days prior to the first dose of lorlatinib.

a. Known strong CYP3A inhibitors (e.g., strong CYP3A inhibitors: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, ritonavir alone and with danoprevir or elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir, troleandomycin, and voriconazole. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

b. Known CYP3A substrates with narrow therapeutic index, such as astemizole*, terfenadine*, cisapride*, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil, fentanyl (including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) (*withdrawn from US market).

c. Known strong CYP3A inducers (e.g., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John’s Wort). d. Known P-gp substrates with a narrow therapeutic index (e.g., digoxin).

8. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

9. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

5. TREATMENT

5.1 Treatment Administered

A patient must sign an informed consent form (ICF) before being evaluated for study entry. Once a patient who has met inclusion and exclusion criteria has provided a signed ICF, will receive lorlatinib orally 100 mg QD, administered as 4 x 25 mg oral tablets, at approximately the same time of the day on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. A dosing card will be provided to the patients to provide guidance for the correct use of lorlatinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and Case Record Forms (CRFs). Lorlatinib will be administered from the date of first dosing (Cycle 1 Day 1 [C1D1]) or until 1 of the following criteria was met (whichever occurred first): disease progression; initiation of a new anti-cancer therapy; unacceptable toxicities; global deterioration of health-related symptoms; pregnancy; withdrawal of consent; loss to follow-up; death; investigator decision dictated by protocol compliance; study termination by the investigator. Since no clinically meaningful effect of food on the PK of lorlatinib has been observed, lorlatinib can be administered with or without food.

After lorlatinib treatment for 4 weeks, patients will receive a lipid level measurement, and the investigator will evaluate patients' will to decide and choose hyperlipidemia therapy. The patients should continue lorlatinib treatment without dose reduction and will receive imaging assess per 8-12 weeks. Subjects who receive hyperlipidemia therapy must observe the therapeutic plan and complete the process under the direction of investigators. They shouldn't use other drugs and methods that may influence the effects of investigational therapeutic mode.

5.2 Hyperlipidemia drugs

Statins: Statins (room temperature) are fundamental in lipid management, primarily used to lower low-density lipoprotein cholesterol (LDL-C).

Medication	Starting Dose	Maximum Dose
Rosuvastatin	5-10 mg/day	40 mg/day
Simvastatin	10-20 mg/day	40 mg/day
Pitavastatin	1-2 mg/day	4 mg/day

Ezetimibe: A Cholesterol Absorption Inhibitor. Ezetimibe (room temperature) inhibits cholesterol absorption and can be combined with statins to further reduce LDL-C levels.

Medication	Recommended Dose
Ezetimibe	10 mg/day

PCSK9 Inhibitors: For Severe Hypercholesterolemia

PCSK9 inhibitors are used for severe hypercholesterolemia or when statins and ezetimibe fail to achieve target LDL-C levels.

Medication	Recommended Dose	Usage Instructions
Evolocumab (Store refrigerated at 2°C–8°C in original carton. Do not freeze/shake. Single-use pens may be kept at room temperature (max 30°C) for up to 48 hours)	140 mg every 2 weeks; 420 mg per month	Subcutaneous injection

Dose Adjustment for Adverse Reactions:

Intervention Group (Rosuvastatin + Ezetimibe + Evolocumab):

Rosuvastatin:

- If a patient experiences mild adverse reactions such as mild myalgia or transaminase elevation (less than 3 times the upper limit of normal), continue current dosage and closely monitor. If symptoms persist or worsen, consider reducing the dose by 10-20% and re-evaluate after 2-4 weeks.
- In cases of moderate to severe myalgia, rhabdomyolysis (creatine kinase levels more than 10 times the upper limit of normal), or significant liver dysfunction (transaminase elevation more than 3 times the upper limit of normal with symptoms or more than 5 times without symptoms), discontinue rosuvastatin

immediately. Once symptoms resolve and laboratory parameters normalize, consider re-initiating at a lower dose (e.g., 50% of the original dose) or switch to an alternative statin if appropriate.

Ezetimibe:

- For mild gastrointestinal discomfort or elevation in liver enzymes (less than 3 times the upper limit of normal), maintain the current dose and monitor closely. If symptoms or liver enzyme elevation persist or worsen, reduce the dose by 50% and reassess after 2-4 weeks.
- If there is evidence of severe liver injury (transaminase elevation more than 5 times the upper limit of normal) or other serious adverse reactions, discontinue ezetimibe and consider alternative lipid-lowering therapies.

Evolocumab:

- Monitor for injection site reactions. Mild local reactions such as redness, swelling, or pain at the injection site that do not interfere with daily activities can be managed with symptomatic treatment and continued use. If reactions are moderate to severe and affect the patient's quality of life, consider reducing the frequency of administration (e.g., from every 2 weeks to every 4 weeks) after consulting with the medical team.
- In rare cases of severe allergic reactions (e.g., anaphylaxis), discontinue evolocumab immediately and provide appropriate emergency treatment. Re-challenge is generally not recommended.

Control Group (Rosuvastatin + Ezetimibe):

- **Rosuvastatin:** Follow the same dose adjustment guidelines as described above for the intervention group.
- **Ezetimibe:** Follow the same dose adjustment guidelines as described above for the intervention group.

Data Collection and Follow-Up for Adverse Events and Dose Adjustments:

- Patients will be closely monitored for any adverse reactions related to the lipid-lowering medications throughout the study period. Any adverse events, regardless of severity, will be documented in detail, including the date of onset, duration, severity (graded according to the Common Terminology Criteria for Adverse Events [CTCAE]), and any associated symptoms.
- For each adverse event, the investigator will assess the relationship to the study medication and determine the appropriate course of action, which may include dose adjustment, temporary or permanent discontinuation of the medication, or initiation of supportive treatment.

- In cases where a dose adjustment is made due to an adverse reaction, the reason for the adjustment, the new dose, and the patient's response to the adjusted dose will be recorded. Follow-up assessments will be conducted at more frequent intervals until the adverse event resolves or stabilizes.
- Patients will be instructed to report any new or worsening symptoms immediately to the study team. The study team will also regularly inquire about the patient's well-being and any potential side effects during follow-up visits.
- Data on all dose adjustments, including the reason for the adjustment, the date of the adjustment, and the patient's lipid levels and clinical status before and after the adjustment, will be collected and analyzed as part of the safety evaluation.

Informed Consent and Patient Education:

- Before enrolling in the study, patients will receive detailed information about the study objectives, procedures, potential risks and benefits, and the importance of adhering to the study protocol. They will be informed about the possibility of adverse reactions and the need for dose adjustments, as well as the measures in place to ensure their safety.
- Patients will be educated on how to recognize and report adverse events and will be provided with a contact number for the study team in case of any concerns or emergencies.

6. STUDY PROCEDURES

All assessments and procedures during the study are detailed in the Schedule of Activities (**Table 1**).

To allow for subject and investigator schedules, holidays, and weather or other emergencies requiring clinical facilities to be closed, all subject visits can be performed within -4/+2 days of the scheduled visit date. To allow for additional flexibility in scheduling subject visits and procedures, Screening and Baseline procedures may be completed on the same day. In that case, treatment must start one day after screening/baseline procedures but within three days. Baseline and Cycle 1 Day 1 procedures may be completed on the same day. However, screening assessments for *eligibility* MUST have already been completed by the preceding day. Screening, baseline and Cycle 1 Day 1 cannot be completed all together on the same day.

6.1 Screening and Informed Consent

Patients with the following will be pre-identified:

- Subjects who have newly diagnosed stage III-IV NSCLC;
- Subjects with an ALK-fusion positive mutation based on assessment as part of the standard of care for this disease;
- Subjects who have adenocarcinoma or its pathologically accepted variants.
- Subjects who have received lorlatinib as 1L treatment.
- Subjects who have hyperlipidemia induced by lorlatinib (G1-G3).
- Subjects meeting the above criteria must provide written informed consent prior to any study-specific procedures being performed.

6.2 Baseline

For both **Part A (real-world study)** and **Part B (randomized controlled trial)**, the following assessments and procedures will be conducted at baseline:

- **Eligibility confirmation** and informed consent
- **Documentation of lorlatinib use** and evaluation of lipid profile
- **Assessment of lorlatinib-associated hyperlipidemia**
- **Recording of cardiovascular risk factors** and lipid management history
- **Randomization** (Part B only): Eligible patients will be randomly assigned to the intervention or control arm

In **Part A**, the initial lipid-lowering strategy (if any) will be documented based on real-world clinical decisions.

In **Part B**, treatment allocation will be as follows:

- **Intervention Group**: Rosuvastatin + Ezetimibe + Evolocumab
- **Control Group**: Rosuvastatin + Ezetimibe

6.3 Study Period

Part A:

Patients will be followed at Week 4, Week 8, Week 20, and Week 24 to monitor lipid levels (TC, LDL-C, HDL-C, TG) and document any changes in lipid-lowering strategies as available.

- At Week 4: If LDL-C remains elevated, the statin dose may be increased or ezetimibe added.

- At Week 8: If LDL-C is still inadequately controlled, PCSK9 inhibitor (e.g., evolocumab) may be introduced.
- If LDL-C is adequately controlled, follow-up frequency may be reduced to every 3 months. All changes in medication, adherence, and tolerability will be documented at each visit.

Part B:

Patients will be monitored every 4 weeks for lipid levels and treatment adherence.

- Primary endpoint: Change in LDL-C from baseline to Week 12
- Secondary endpoints: Percentage changes in other lipid parameters and longitudinal trends over 24 weeks

End of Treatment Visit (Week 24 or Early Termination)

At the final visit (Week 24 or early discontinuation), the following assessments will be performed for both Part A and Part B:

- Final **lipid profile evaluation**
- **Documentation of final lipid-lowering regimen**
- **Assessment of treatment tolerability and adverse events**
- For **Part B**, summary comparison of LDL-C reduction and treatment adherence between groups
- **Study completion procedures** including return of unused medications (if applicable), and final documentation

Follow-up

There will be **no post-treatment follow-up** mandated beyond Week 24 for either part of the study unless clinically indicated.
For patients continuing lorlatinib and lipid-lowering therapies as part of routine care, standard lipid monitoring is recommended every 3 months according to guidelines.

Subject Withdrawal

Subjects may be withdrawn from the study at any time under the following conditions:

- **Voluntary withdrawal** of consent by the subject.
- **Investigator decision** due to safety concerns, protocol non-compliance, or intercurrent illness.
- **Loss to follow-up** despite reasonable efforts to recontact the subject.
- **Adverse events** that warrant discontinuation of lipid-lowering or lorlatinib therapy.

All reasons for withdrawal will be documented. If possible, an early termination visit will be conducted to perform end-of-treatment assessments.

7. ASSESSMENTS

7.1 Efficacy and Management Assessments

Part A (Real-World Study):

- Hyperlipidemia Management Strategy Documentation: At baseline and each follow-up visit (Weeks 4, 8, 20, and 24), lipid-lowering strategies initiated in response to lorlatinib-associated hyperlipidemia will be recorded. Management patterns will be categorized based on treatment class (e.g., statins, ezetimibe, PCSK9 inhibitors), monotherapy versus combination therapy, timing of initiation, dose adjustments, and adherence to standard guideline recommendations. The primary endpoint for Part A is a descriptive analysis of these lipid-lowering strategies in stage IIIB–IV ALK-positive NSCLC patients receiving first-line lorlatinib.

Part B (Randomized Controlled Trial):

- Lipid Panel Monitoring: Blood samples will be collected at baseline and Weeks 4, 8, 12, 20, and 24 for measurement of lipid parameters, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).
- The primary endpoint in Part B is the mean percentage change in LDL-C from baseline to Week 12.
- Secondary efficacy assessments include:
    - Mean and median changes from baseline in TC, TG, LDL-C, and HDL-C at Weeks 12 and 24.
    - Between-group comparisons (intervention vs. control) using repeated measures ANOVA or equivalent statistical methods.

7.2 Exploratory Assessments

- Endothelial Function Assessment: In a subset of patients, brachial artery flow-mediated dilation (FMD) will be evaluated at baseline and within 24 weeks of treatment to explore the vascular effects of lorlatinib-associated dyslipidemia and lipid-lowering interventions. Measurements will be performed using standard ultrasound-based techniques, with all imaging centrally reviewed by trained evaluators blinded to treatment allocation (Part B). The change in FMD will be assessed as an exploratory endpoint.

7.3 Safety Assessments

- Adverse events (AEs) and serious adverse events (SAEs) will be recorded throughout the study duration (baseline to Week 24).

- Laboratory safety tests (including liver function, renal function, and lipid profiles) will be monitored regularly.
- For Part B, tolerability and adherence to lipid-lowering agents (e.g., statin-related muscle symptoms, injection site reactions for PCSK9 inhibitors) will be assessed at each visit.

8. ADVERS`E EVENT REPORTING

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the Sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

9. DATA ANALYSIS/STATISTICAL METHODS

- All data collection will be done using the LinkDoc data management platform. Data will be entered and managed in a secure and compliant manner, with appropriate backup and access controls.
- Regular data quality checks will be performed to ensure the accuracy and completeness of the data. Any discrepancies or missing data will be resolved promptly through communication with the study sites.

10. STUDY ORGANISATION AND COMMITTEES

10.1 Study Coordination

The study is an investigator-initiated trial conducted by Lung Cancer Research Centre Sun-Yat Sen University Cancer Center.

10.2 Trial Management Committee

The Trial Management Committee will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

11. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Sponsor or companies working with or on behalf of Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

12. ETHICS

- The study protocol will be reviewed and approved by the appropriate ethics committees before commencing the study.
- An independent data monitoring committee will be established to oversee the safety and progress of the study. The DMC will conduct periodic reviews of the data and make recommendations regarding the continuation, modification, or termination of the study based on the safety and efficacy findings.

13. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, change in benefit/risk profile, or at the discretion of the Sponsor.

If the study is prematurely terminated or discontinued, the Sponsor will promptly notify the investigators. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 2 weeks. As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

14. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

14.1 Communication of Results by the Sponsor

The Sponsor shall fulfill its commitment to publicly disclose clinical study results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov).

14.2 Publications by Investigators

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

The investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is defined in the Clinical Study Agreement between the Sponsor and the institution. In this section, entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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APPENDIX 1 ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
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	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.