# Efficacy and Safety of Apatinib in Combination with Ifosfamide and Etoposide Versus Ifosfamide and Etoposide Alone in the Treatment of Relapsed or Refractory Osteosarcoma which Progressed Upon First-Line Chemotherapy: A Multicenter, Randomized, Prospective Clinical Study

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**Version History/Amendment History**

| Version No. | Version Date | Summary of Major Changes |
|---|---|---|
| **1.0** | **20210825** | Not applicable |
| **2.0** | **20211027** | ● Change section 4.3.3 "Prohibited and Restricted Prohibitions" to "Prohibited Combined Treatments". The specific changes are as follows:<br>• Biological treatments with anti-tumor effects (excluding cytokines used for the treatment of adverse events caused by chemotherapy), as well as traditional Chinese medicinal products and traditional Chinese medicines with anti-tumor effects;<br>• Drugs with immunomodulatory effects, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulins, gamma globulin) and traditional Chinese medicinal products with immunomodulatory effects.<br>• Radiotherapy for controlling neoplasm (palliative radiotherapy, such as radiotherapy to alleviate pain from bone metastasis or symptoms of brain metastasis, is permitted as long as it is not directed at the target lesion);<br>According to the investigator's assessment, subjects who need to undergo clinical treatment using any of the above-mentioned methods should be excluded from the study. Subjects can receive other drug therapies that the investigator deems medically necessary.<br>● Supplement the basis for sample size calculation:<br>This study is a prospective, two-arm, multicenter, open-label clinical study. Currently, there is a lack of internationally recognized objective mPFS data for progressive relapsed or refractory osteosarcoma after traditional chemotherapy. The large difference in objective response rates |

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| | | after first-line chemotherapy and second-line chemotherapy makes it difficult to estimate the sample size for this study. However, based on the published retrospective data in the past three years by the Bone Neoplasm Department of Peking University People's Hospital and Peking University Shougang Hospital, we set the mPFS of 5 months (null hypothesis) obtained from the IE chemotherapy for progressive relapsed or refractory osteosarcoma as the underlying target, and expect to reach a mPFS of 11 months or higher (alternative hypothesis) as the target value. This study uses two-sided design, with $\alpha$=0.05 (two-sided), $\beta$=0.20 (power=80%), assuming that it will take 18 months to complete enrollment, with a follow-up period of 12 months. Patients will be enrolled at a 2:1 ratio with a dropout rate of 10%, the control group needs 26 patients, and the test group needs 52, with a total of 78 patients. |
| **3.0 (Final version before enrolment)** | **20211208** | ● Modify the drug washout period. "In this study, the pretreatment washout period for general chemotherapy drugs is 2 weeks (for the previous chemotherapy with liposomal doxorubicin, a 3-week washout period is required)" is changed to: In this study, the pretreatment washout period is 3 weeks.<br>● "For participants in the control group, the safety follow-up period is 21 days (±5 days) after the last administration; thereafter, the same arrangement as the trial group is followed." Change to: "For participants in the control group, the safety follow-up period is 30 days (±5 days) after the last administration."<br>● "All subjects are allowed to receive subsequent local treatments (including surgery or stereotactic surgery, etc.) after completing 10 cycles of treatment, to treat primary or postoperative local relapsed neoplasm and distant metastasis, or to continue systemic therapy (including continued apatinib treatment and/or combined IE chemotherapy)." Change to: "All subjects are allowed to receive |

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| | | subsequent local treatments (including surgery or stereotactic surgery, etc.) after disease progression or intolerable toxicity, to treat primary or postoperative local relapsed neoplasm and distant metastasis, or to continue systemic therapy (including continued apatinib treatment and/or combined IE chemotherapy)." |
| **4.0** | **20220526** | ● Add inclusion criteria: Cardiac function Doppler ultrasound evaluation, i.e., electrocardiogram examination is normal or abnormal without clinical significance, and the cardiac ultrasound shows the left ventricular ejection fraction (LVEF) ≥ lower limit of normal (50%).<br>● "Participants must undergo radiological imaging assessment of the disease within 2 weeks before medication, including CT or MRI of bone and soft tissue tumor sites, chest CT plain scan or enhancement, abdominal CT plain scan or enhancement, ECT whole-body bone imaging or whole-body PET/CT." Change to: "Subjects must undergo radiographic assessment of the disease, including CT or MRI of bone and soft tissue neoplasm sites, chest CT plain scan or enhanced scan, and abdomen CT plain scan or enhanced scan within 2 weeks before dosing, and ECT whole body bone imaging or whole body PET/CT within 3 months before dosing."<br>● "For subjects who experience partial responses (PR) or stable disease (SD), the subjects in the test group will be advised to continue oral apatinib until disease progression." Change to: "For subjects who experience partial responses (PR) or stable disease (SD), the subjects in the test group will be advised to continue oral apatinib until disease progression or intolerable toxicity occurs, for a maximum of 1 year; while the subjects in the control group may continue follow-up, with the follow-up period and method the same as those during the treatment phase, until disease progression occurs, for a maximum |

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| | | of 1 year, after which they will withdraw from the group and switch to other treatments.” |
| **4.1** | **20220930** | Add Co-principal investigator, Professor Lu Xie |

**Signature Page**

**Signature of Principal Investigator (Leading center)**

I will conscientiously perform the responsibilities of the investigator and personally participate in or direct this clinical study in accordance with the provisions of GCP in China. We have read and confirmed this protocol. I agree to perform relevant responsibilities in accordance with Chinese law, the Declaration of Helsinki, Chinese GCP and this protocol. The amendment to the protocol can only be implemented with the consent of the Ethics Committee (EC), unless measures must be taken to protect the safety, rights and interests of subjects.

**Study Institution:** Peking University People's Hospital

| **Wei Guo, Lu Xie** | Wei Guo / Lu Xie | 30th/9/2022 |
|---|---|---|
| **Principal Investigator (Printed)** | **Principal Investigator (Signature)** | **Signing date (Day/Month/Year)** |

**Signature Page**

**Signature of Principal Investigator (Paiticipating center)**

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**Study Institution:** Jinling Hospital, Nanjing University

| **Guangxin Zhou** | Guangxin Zhou | 30/09/2022 |
|---|---|---|
| **Principal Investigator (Printed)** | **Principal Investigator (Signature)** | **Signing date (Day/Month/Year)** |

**Signature Page**

**Signature of Principal Investigator (Paiticipating center)**

I will conscientiously perform the responsibilities of the investigator and personally participate in or direct this clinical study in accordance with the provisions of GCP in China. We have read and confirmed this protocol. I agree to perform relevant responsibilities in accordance with Chinese law, the Declaration of Helsinki, Chinese GCP and this protocol. The amendment to the protocol can only be implemented with the consent of the Ethics Committee (EC), unless measures must be taken to protect the safety, rights and interests of subjects.

**Study Institution:** Shanghai Bone Tumor Institute, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine

| **Yingqi Hua** | Yingqi Hua | 30/09/2022 |
|---|---|---|
| **Principal Investigator (Printed)** | **Principal Investigator (Signature)** | **Signing date (Day/Month/Year)** |

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Outline

## 1. Study Synopsis

This study adopts a multicenter, randomized, prospective clinical study design. The enrolled patients will either receive oral apatinib in combination with intravenous ifosfamide and etoposide (IE) chemotherapy or IE chemotherapy alone. This study aims to evaluate the efficacy, safety, and impact on survival of apatinib in combination with IE versus IE chemotherapy alone in the treatment of relapsed or refractory osteosarcoma which progressed upon first-line chemotherapy (or relapsed within 6 months after completion of adjuvant chemotherapy). The study is a multicenter clinical trial, with $\alpha$=0.05 (two-sided) and power=0.8. The estimated sample size is 78 patients, who will be randomly assigned at a 2:1 ratio to either the apatinib + IE group or the IE group using a static randomization table.

## 2. Study Background

Osteosarcoma is a malignant neoplasm originating from mesenchymal tissue, which is highly invasive and prone to hematogenous metastasis [1, 2]. Currently, standard first-line chemotherapy regimen includes sequential chemotherapy with doxorubicin, cisplatin, high-dose methotrexate (HD-MTX), with or without ifosfamide (IFO) [3], upon which the overall 5-year survival rate for treatment-naïve localized osteosarcoma could reach 67.7% according to 2015 SEER data [4]. For those who progressed upon first-line chemotherapy, the overall 5-year survival rate was reported as only 7.9% [5]. Although these patients might undergo aggressive resection of metastatic lesions, the prognosis is still extremely poor, and at this time disease control mainly relies on effective internal medication.

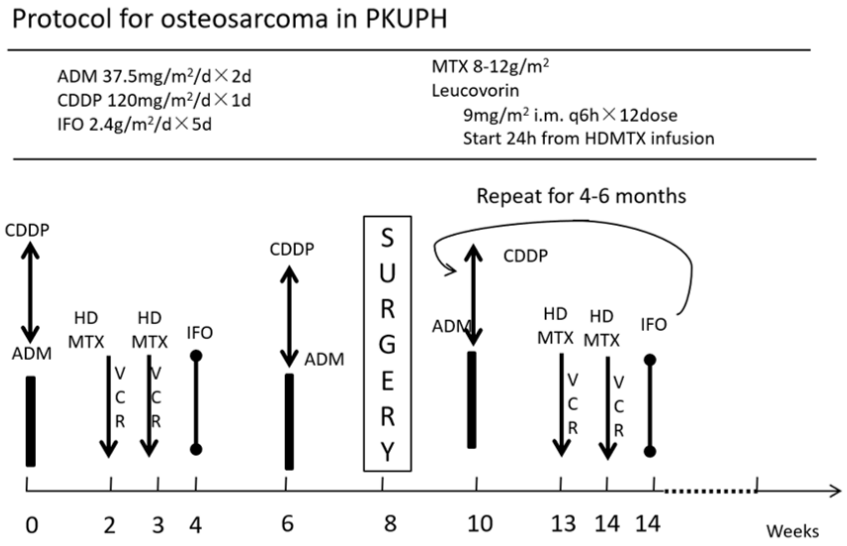


Figure 1: First-line Chemotherapy Protocol for Treatment-Naïve Osteosarcoma at the Musculoskeletal

Tumor Center of Peking University People's Hospital nowadays [6]

Young patients in relapsed/metastatic pattern are often in well physical condition to continue treatment. Therefore, if effective second-linedrugs can be explored, new vitality would be brought to these patients. The principle of osteosarcoma treatment is to perform local therapy based on the underlying stability controlled by medication for at least 2-4 months. As long as there is an opportunity to remove all the visible foci, patients would have a cure chance of 25% or so [7]. The commonly used classic second-lineregimens currently recommended by the National Cancer Comprehensive Network (NCCN) include: high-dose ifosfamide in combination with etoposide (IE regimen: ifosfamide, etoposide) with an effective rate of 30.8% [8], or anti-multitarget kinase inhibitors, such as sorafenib [9], regorafenib [10], apatinib [11] etc.

Over the past 20 years, the development of small molecule tyrosine kinase inhibitors has made significant progress in the field of neoplasms. Angiogenesis is considered an important step in the development of osteosarcoma, and paired studies before and after chemotherapy have shown that chemotherapy can induce the expression of vascular endothelial growth factor receptors (VEGFRs) in osteosarcoma [12]. Basic studies have shown that angiogenic factors and their receptors, including vascular endothelial growth factors (VEGFs), VEGFR1 (flt-1), VEFGR2 (KDR), VEFGR3 (flt-4), etc., are highly expressed on the surface of osteosarcoma cells [1]. In recent years, TKIs covering VEGFRs have achieved promising results in the studies of osteosarcoma, including sorafenib, sunitinib, pazopanib, apatinib, etc. How to choose the appropriate TKI dose and delay the occurrence of drug resistance have become a hot topic in recent years. Table 2 summarizes the results of all prospective clinical trials of anti-angiogenic targeted drugs currently conducted for osteosarcoma. Among them, apatinib is a small molecule VEGFR tyrosine kinase inhibitor, with the chemical name of mesylate N-[4-(cyanocyclopentyl) phenyl]2-[(4-pyridylmethyl)amino](3-pyridyl) formamide (C25H27N5O3S). Pharmacodynamic studies have shown that this compound can inhibit tumor angiogenesis and thus treat neoplasms by inhibiting the VEGFR tyrosine kinase activity (VEGFR-2 high-selective inhibitor) and blocking the signal transduction after the binding of VEGF and VEGFR-2. Preliminary drug studies have shown that apatinib has a stronger inhibitory effect on VEGFR-2 than sorafenib (Table 1.1), and animal studies have shown that apatinib is effective in mouse sarcoma models (Table 1.2). Currently, apatinib has been approved for marketing in China by the National Medical Products Administration, and it is a third-line therapy with indications of digestive tract neoplasms such as gastric cancer and esophageal cancer.

Table 1: Comparison of $IC_{50}$ of Various Tyrosine Kinase Inhibitors (TKIs)

| Target of Drug | $IC_{50}$[1] | | | | |
|---|---|---|---|---|---|
| | Apatinib | Sorafenib | Sunitinib | Pazopanib | Regorafenib |
| VEGFR-1 | 70 | -- | 2 | 10 | 13 |
| VEGFR-2 | 2 | 15 | 10 | 30 | 4.2 |
| VEGFR-3 | -- | 20 | 17 | 47 | 46 |
| PDGFR-β | 537 | 57 | 8 | 84 | 22 |
| c-kit | 420 | 68 | -- | 74 | -- |
| FGFR-1 | >10000 | 580 | -- | -- | 202 |
| FLT-3 | -- | 58 | -- | -- | -- |

[1] Median inhibitory concentration; the concentration that reduces the effectiveness in in-vivo studies by 50%.

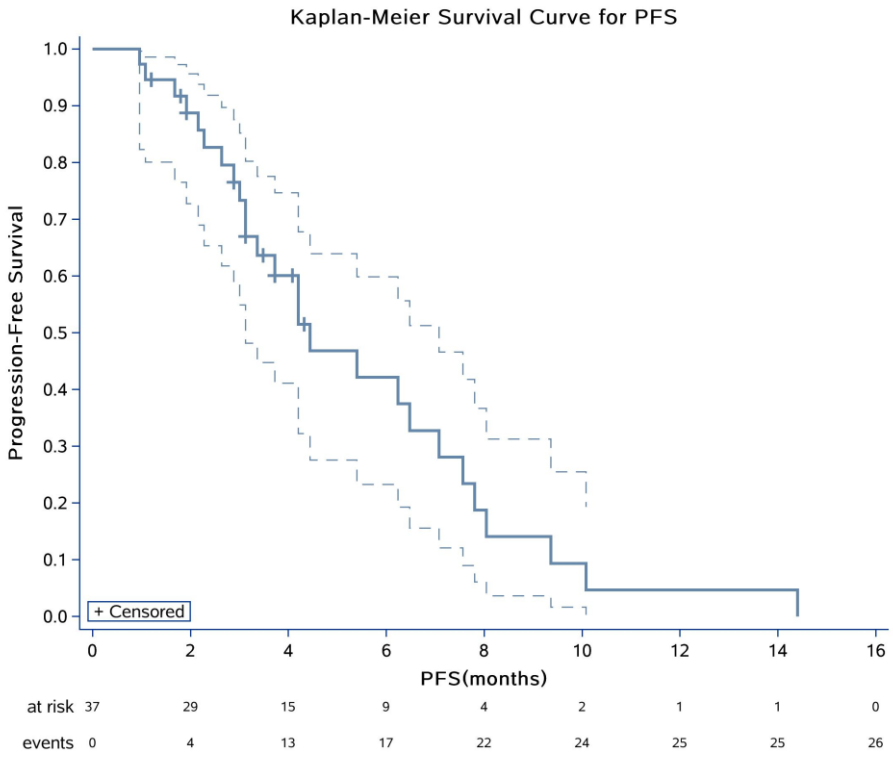


Figure 2: Progression-Free Survival Curve (Kaplan-Meier Curve) of Osteosarcoma Patients Treated with Apatinib Alone Who are Resistant to Chemotherapy.

Peking University People's Hospital had also conducted a prospective, single-center, open-label, single-arm clinical study on apatinib for progressive osteosarcoma which failed after traditional chemotherapy from 2016 to 2017 (clinicaltrials registration number: NCT02711007) [11]. From March 2016 to June 2017, a total

of 41 subjects with progressive osteosarcoma were enrolled, and finally, 37 subjects were included in the analysis. As of the follow-up on 31 Dec 2017, the objective response rate was 43.24% (16/37), and the 4-month progression-free survival rate was 56.75% (95% CI 39.43%-70.84%) (Figure 2). However, only 13/37 (35.14%) of osteosarcoma patients reached 6-month progression-free survival. The median progression-free survival (mPFS) and overall survival (OS) were 4.50 (95% CI 3.47-6.27) months and 9.87 (95% CI 7.97-18.93) months, respectively. In addition, 25/37 (67.57%) of the subjects could not tolerate the toxicity of the drug, leading to dose reduction or suspension, and there was no significant improvement in quality-of-life, with a trend of increased pain in the early stages of treatment. The conclusion of the study was that progressive osteosarcoma that failed traditional chemotherapy was sensitive to apatinib, with a high objective response rate, and the duration of efficacy was similar to that of other anti-angiogenic TKIs. The study found that the main reason for tumor progression was the progression of bone foci. The mPFS for pure lung metastases of osteosarcoma was 6-7 months, while the mPFS for pure bone metastases of osteosarcoma was only 2 months. How to overcome the progression of bone and soft tissue foci in progressive osteosarcoma has become an urgent problem to be solved.

Table 2: Summary of Current Targeted Treatment Clinical Study for Progressive Osteosarcoma

| Index | Apatinib Phase 2 Single-Arm Study N=37 | Apatinib + PD1 Phase 2 Single-Arm Study N=41 | Sorafenib Phase 2 Single-Arm Study N=35 | Regorafenib Phase 2 Study (Regobone) N=26 (randomized controlled study) | Pazopanib Retrospective Study N=15 | Cabozantinib Phase 2 Single-Arm Study N=42 | Lenvatinib Phase 1b Study N=26 |
|---|---|---|---|---|---|---|---|
| PR[1] | 43.2% | 22.0% | 8% | 7.7% | 6.6% | 11.9% | 8% |
| SD[1] | 21.6% | 63.4% | 34% | 57.7% | 40% | 33.3% | 34% |
| Disease control rate | 64.8% | 85.4% | 29% | 75.4% | 46.6% | 45.2% | 42% |
| PFS rate (6 m) | 36.7% | 43.6% | 4m PFS rate 40% | 35% | | 33.3% | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| mPFS | 4.5m | 5.7m | 4m | 4.1m | 6m | 6.2m | 5.5m |

[1] According to the Response Evaluation Criteria in Solid Tumors (RECIST)

At the 2019 European Society for Medical Oncology (ESMO) Annual Meeting, Nathalie Gaspar et al [13] reported a single-arm Phase 1B clinical study of lenvatinib in combination with IE chemotherapy for progressive osteosarcoma in patients aged 2 to 25 years. For the first time, the mPFS of progressive osteosarcoma was extended from 4-6 months to 11 months (95% CI 4.5-12.9 months). Whether this is due to the control of osteosarcoma foci metastasis and progression using combined chemotherapyremains unknown. Peking University People's Hospital also reviewed retrospective case-series from June 2019 to April 2020 and found that for adolescents and adults with a body surface area (BSA) of 1.0 or more, the oral apatinib 500 mg QD in combination with IE (ifosfamide 1.8 g/m$^2$/d $d_{1\text{-}3}$ Q17d+etoposide 100 mg/m$^2$/d $d_{1\text{-}3}$ Q17d) had objective response rate of 50.00% (15/30 subjects) and mEFS of 13.90 (4.96, 22.84) months.

As osteosarcoma is an orphan disease, there are currently no registered phase 3 clinical studies exploring the efficacy of TKIs in combination with IE versus IE chemotherapy in Mainland of China. This study intends to observe the efficacy and safety of apatinib in combination with IE versus IE chemotherapy alone in the treatment of relapsed or refractory osteosarcoma which progressed upon first-line osteosarcoma chemotherapy, which in most part of China Ifosphamide has already been incorporated into first-line chemotherapy through a prospective, open-label, multicenter randomized controlled design. The aim is to evaluate if this combination has superior disease control comparing to traditional IE chemotherapy for thos patients with unresectable large tumor burden and extremely poor prognosis.

## 3. Study Objectives

### Primary Objective

To clarify whether apatinib in combination with IE has a superior mPFS comparing to the IE chemotherapy alone in patients with relapsed or refractory osteosarcoma that progressed upon first-line chemotherapy or relapsed within 6 months after completion of adjuvant chemotherapy.

### Secondary Objectives

1. To evaluate and compare the OS, objective Response Rate (ORR), disease Control Rate (DCR), duration of response (DOR), time to Response (TTR), time to progression (TTP), 4-month PFS rate and 6-month PFS rate, event free survival (EFS) for apatinib in combination with IE versus IE chemotherapy alone

in patients with relapsed or refractory osteosarcoma that progressed upon first-line chemotherapy or relapsed within 6 months after completion of adjuvant chemotherapy.

2. To evaluate and compare the short-term (within 1-2 years) and long-term (within 5-6 years) safety of apatinib in combination with IE versus IE chemotherapy alone in patients with relapsed or refractory osteosarcoma that progressed upon first-line chemotherapy or relapsed within 6 months after completion of adjuvant chemotherapy. The safety of the drug will be evaluated according to the NCI-CTC AE 5.0.
3. To evaluate and compare the quality-of-life scores for apatinib in combination with IEversus IE chemotherapy alone in patients with relapsed or refractory osteosarcoma that progressed upon first-line chemotherapy using EORTC QLQ-C30 questionnaire.

## 4. Study Design

### 4.1 Type of Study Design and Study Subjects

This study adopts a multicenter, randomized, prospective clinical study design.

### 4.2 Study Subjects

The study subjects are patients with relapsed or refractory osteosarcoma that progressed upon first-line chemotherapy.

### 4.3 Criteria for Selecting Study Subjects

#### 4.3.1 Inclusion Criteria

Potential subjects must meet all of the following criteria to be selected for this study. If there are multiple clinical laboratory test results during the screening phase, the result closest to the dosing date should be used to prove the subject's eligibility for this study.

1. Patients aged 12 years and above, but under 65 years, regardless of gender, with a BSA of more than 1.0 $m^2$.

2. Progressive relapsed or refractory osteosarcoma confirmed by histopathology. A pathological diagnosis must be obtained for patients with local neoplasms and isolated pulmonary foci, while multiple pulmonary metastases do not require a pathology examination. (Definition of progressive osteosarcoma: (1) The primary neoplasm or local relapsed neoplasm cannot be cured by surgery or other local treatment methods, such as stereotactic radiosurgery, argon-helium knife, focused ultrasound knife, etc., or the patient refuses surgery or other local treatments. (2) Distant metastasis has occurred, and the metastatic neoplasm cannot be cured by surgery or other local treatment methods, such as: stereotactic radiosurgery, argon-helium knife, focused

ultrasound knife, etc., or the patient refuses surgery or other local treatments.)

3. Osteosarcoma that progressed after standard, full-dose first-line chemotherapy, or relapsed within 6 months after stopping the chemotherapy. (First-line chemotherapy drugs include three or more of the following: high-dose methotrexate, anthracyclines, cisplatin, ifosfamide)

4. ECOG performance status score [14-16] of 0-1, with an expected survival period of more than 3 months.

5. Patients who have recovered from previous treatment, i.e., according to NCI-CTCAE version 5.0, all adverse events (except for alopecia) have subsided to Grade 1 or below.

6. The following peripheral blood profile and blood chemical indicators suggest appropriate organ function:

✓ Haemoglobin (Hb) ≥ 90 g/L,

✓ Absolute neutrophil count (ANC) ≥ $1.5\times10^9$/L,

✓ Platelet count (PLT) ≥ $80\times10^9$/L,

✓ Serum creatinine (Cr) ≤ 1.5× upper limit of normal (ULN), blood urea nitrogen (BUN) ≤ 2.5×ULN;

✓ Total bilirubin (TB) ≤ 1.5×ULN;

✓ Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5×ULN; in case of metastases to the liver, AST and ALT ≤ 5.0×ULN.

✓ Albumin (ALB) ≥ 25 g/L;

✓ International normalized ratio (INR) ≤ 1.5, prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5×ULN;

✓ Protein urine < 2+; if protein urine ≥ 2+, the 24-hour protein urine quantification must show protein ≤ 1 g.

✓ Thyroid-stimulating hormone (TSH) ≤ ULN; if abnormal, the T3 and T4 levels should be examined, and patients with normal T3 and T4 levels can be included in the study.

✓ Cardiac function Doppler ultrasound evaluation, i.e., electrocardiogram examination is normal or abnormal without clinical significance, and the cardiac ultrasound shows the left ventricular ejection fraction (LVEF) ≥ lower limit of normal (50%).

7. Women of childbearing age should agree to use contraception measures (such as intra-uterine device [IUD], contraceptive, or condom) during the study and within 6 months after the end of the study; they must have a negative serum or urine pregnancy test result within 7 days before enrollment, and must be non-lactating; men should agree to use contraception measures during the study and within 6 months after the end of the study.

8. Patients (or their legal representative) should sign the informed consent form (ICF), to demonstrate their understanding of the purpose of this study and the procedures required by the study, and their willingness to participate in this study.

**4.3.2 Exclusion Criteria**

Potential subjects who meet any of the following criteria must be excluded from the study:

1. Previous exposure to small molecule TKIs that inhibit angiogenesis, such as anlotinib, apatinib, pazopanib, sorafenib, etc., or previous use of IE chemotherapy alone.
2. Systemic cytotoxic drug therapy or radiotherapy within 3 weeks.
3. Other malignant neoplasm diagnosed within the past 3 years, excluding cured skin basal cell carcinoma, cervical carcinoma in situ, and breast cancer with no recurrence >3 years after radical surgery.
4. Obvious symptoms of metastases to the central nervous system, such as headaches, brain oedema, blurred vision, etc.
5. Uncontrolled hypertension (blood pressure systolic ≥ 140 mmHg or blood pressure diastolic ≥ 90 mmHg, despite using optimal drug therapy).
6. Presence of poorly controlled cardiac clinical symptoms or diseases, such as: (1) Cardiac failure of NYHA class 2 or above; (2) Angina unstable; (3) Myocardial infarction occurred within the past 6 months; (4) Clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention; (5) QTc interval ≥ 450 ms in males, ≥ 470 ms in females; (6) Clinically significant pericardial disease, or electrocardiogram indicating acute ischaemia or active conduction system abnormalities.
7. Uncontrolled comorbidities, including but not limited to: poorly controlled diabetes mellitus, persistent active infection, or mental illnesses or social conditions that may affect the subject's compliance with the study.
8. A history of hereditary or acquired haemorrhagic disorders or coagulation dysfunction (such as haemophilia, coagulation disorders, reduced platelets, hypersplenism, etc.); clinically significant haemorrhagic symptoms or a clear haemorrhagic diathesis, such as gastrointestinal haemorrhage, haemorrhagic gastric ulcer, etc., within 3 months before the first dose of study drug; abnormal coagulation function (INR > 1.5, or prothrombin time (PT) > ULN+4 seconds, or APTT > 1.5 ULN), with a haemorrhagic diathesis or with current thrombolysis therapy, anticoagulant therapy, or antiplatelet therapy.

9. Manifest haemoptysis or daily haemoptysis volume of 2.5 ml or more within 2 months prior to enrollment.
10. A history of drug abuse related to mental substances which can not be quitted, or presence of a mental disorder.
11. Presence of an open wound or fracture within 3 weeks prior to enrollment.
12. A major surgery within 3 weeks prior to enrollment.
13. Factors that have a manifest impact on the absorption of orally administered drugs, such as inability to swallow, chronic diarrhoea, and intestinal obstruction.
14. Sinus or perforation of a hollow organ within the past 6 months.
15. A evidence showing a history or current presence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-induced pneumonia, and serious impairment of lung function, etc.
16. Hepatitis B viral or hepatitis C, or active infection requiring antimicrobial treatment (for example, requiring the use of antibacterial drugs, antiviral drugs, or antifungal treatment).
17. Patients who have participated in other clinical studies of antineoplastic agents within the past 4 weeks.
18. Patients who have received treatment with a potent CYP3A4 inhibitor within 7 days, or a potent CYP3A4 inducer within 12 days prior to participating in the study.
19. Known abnormal reactions, hypersensitivity, or intolerance to apatinib, IE chemotherapy, or their excipients.
20. Current use of other antineoplastic agents.
21. Patients who have undergone radiotherapy on the target lesion under observation, which has not progressed after the treatment.
22. Patients who have received a vaccine during the treatment process, or those who have received an adenovirus vaccine within 4 weeks.
23. The investigator believes that there may exist any conditions that could harm the patient or cause the patient to be unable to meet the study requirements or carry out the study procedures.

**4.3.3 Prohibited Concomitant Treatments**

• Biological treatments with anti-tumor effects (excluding cytokines used for the treatment of adverse events caused by chemotherapy), as well as traditional Chinese medicinal products and traditional Chinese medicines with anti-tumor effects;

• Drugs with immunomodulatory effects, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulins, gamma globulin) and traditional Chinese medicinal products with immunomodulatory effects.

• Radiotherapy for controlling neoplasm (palliative radiotherapy, such as radiotherapy to alleviate pain from bone metastasis or symptoms of brain metastasis, is permitted as long as it is not directed at the target lesion);

According to the investigator's assessment, subjects who need to undergo clinical treatment using any of the above-mentioned methods should be excluded from the study. Subjects can receive other drug therapies that the investigator deems medically necessary.

**4.3.4 Withdrawal Criteria**

The criteria for a subject to withdraw from the study treatment are as follows:

1. The subject requests study drug discontinuation;

2. Medical imaging or clinical features indicate disease progression, unless the subject meets the criteria for continued treatment after progression (see Table 5.3 for details);

3. During the course of the study, the subject experienced a pregnancy event.

4. Any clinical adverse event, laboratory test abnormality, or other medical conditions occur, which may result in the subject no longer benefiting from continued treatment.

5. The subject has comprehensive deterioration of health status and is unable to continue participation in the study;

6. Marked protocol deviations (such as the subject is unqualified) are discovered after enrollment.

7. The subject is lost to follow-up;

8. Jiangsu Hengrui Pharmaceuticals Co., Ltd. (hereinafter referred to as the "Company") decides to discontinue the study.

For each subject who withdraws from the study, the investigator is required to record all required details, withdrawal date, and reasons for withdrawal in the Case Report Form (CRF).

**4.3.5 Removal Criteria**

1. After enrollment, it is discovered that the subject does not meet all inclusion criteria or meet any exclusion criterion.

2. The subject has used prohibited drugs or prohibited concomitant treatments in this study.

3. The subject violates the clinical study protocol.

#### 4.3.6 Subsequent Treatments

All subjects are allowed to receive subsequent local treatments (including surgery or stereotactic surgery, etc.) after disease progression or intolerable toxicity, to treat primary or postoperative local relapsed neoplasm and distant metastasis, or to continue systemic therapy (including continued apatinib treatment and/or combined IE chemotherapy).

### 4.4 Grouping of Study Subjects

In this study, the enrolled patients are divided into two groups to receive oral apatinib in combination with intravenous IE or IE chemotherapy alone.

### 4.5 Study Process

#### 4.5.1 Study Procedures

The entire study includes the screening phase, treatment phase, and follow-up phase. All subjects in the study need to meet all inclusion criteria and do not meet any exclusion criterion.

During the screening phase, potential subjects will undergo an eligibility assessment for the study after signing the ICF. The screening phase does not exceed 14 days, and qualified subjects will enter the treatment phase after completing the screening investigation and assessment, and follow the protocol for study treatment and visits. Subjects must undergo radiographic assessment of the disease, including CT or MRI of bone and soft tissue neoplasm sites, chest CT plain scan or enhanced scan, and abdomen CT plain scan or enhanced scan within 2 weeks before dosing, and ECT whole body bone imaging or whole body PET/CT within 3 months before dosing. Subsequent radiographic assessments must be consistent with baseline. During the treatment phase, radiographic assessments will be conducted once every two cycles, mainly including chest CT plain scan or enhanced scan, plain film and CT or MRI plain scan of bone and soft tissue neoplasm sites. Whole body bone scan or PET/CT examination should be conducted every 6 months. After the end of the treatment phase, radiographic assessments will continue to be performed once every 2 months until disease progression occurs, the subject begins subsequent anti-tumor treatment, the study ends, or the subject dies. Radiographic assessments will be conducted according to the RECIST v1.1, and the radiographic evaluation of tumor efficacy will be conducted by the investigator at the study site. Subsequent treatments can only begin after there is evidence of disease progression.

In this study, the pretreatment washout period is 3 weeks. All adverse events (AEs) occurring within the following time period should be reported: from the subject's signing of the ICF to 4 weeks after the last administration of the study drug. The treatment phase is scheduled to be 10 cycles. If the subject has not

experienced tumor progression by the end of the treatment phase, the investigator will decide on subsequent treatment based on the subject's benefit. For subjects who experience complete responses (CR), they may try to discontinue the study drug for follow-up, or may continue oral apatinib. For subjects who experience partial responses (PR) or stable disease (SD), the subjects in the test group will be advised to continue oral apatinib until disease progression or intolerable toxicity occurs, for a maximum of 1 year; while the subjects in the control group may continue follow-up, with the follow-up period and method the same as those during the treatment phase, until disease progression occurs, for a maximum of 1 year, after which they will withdraw from the group and switch to other treatments. The safety follow-up period for the test group is 30 days (±5 days) after the last dose of apatinib, during which, subjects should go to the study site for a safety examination at the first safety follow-up visit; the second and third safety visits are telephone visits. The safety follow-up period for control group is 30 days (±5 days) after the last administration. After the safety follow-up period ends, the subjects will enter the survival follow-up period, which will last until the subject's death, loss to follow-up, withdrawal of consent, or discontinuation of the study by company. During this period, starting from the end of the last study treatment, follow-up will be conducted once every 2 months until the clinical cut-off date, for collecting survival information and subsequent anti-tumor treatment information.

**4.5.2 Study Design Process**

1. The study plans to recruit 78 subjects from 31 Mar 2022 to 30 Sep 2024.
2. The initial assessment will be conducted after 2 cycles of drug administration, followed by assessments every 2 cycles. All subjects will be assessed, including those who discontinued the study drug prior to disease progression.
3. The visit after treatment discontinuation should be completed within 4 weeks after the treatment is stopped or the subject withdraws from the study.
4. Follow-up on survival status and subsequent anti-tumor treatment will be conducted every 2 months, with a follow-up period of 1 year.

**4.5.3 Schedule of Activities**

Table 3.3.1 Schedule of Activities

| **Assessment/Time (21 days per cycle)** | **Screening Phase D-14~D-1** | **Treatment Phase** | | | | | | **Monotherapy Maintenance Phase** | **Safety Follow-up** | | **Survival Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1** | | | **Cycle 2 and Thereafter** | | | | | | |
| | | **D1** | **D8** | **D15** | **D1 Once per cycle** | **D8** | **D15** | One year after the initiation of treatment, or upon disease progression / intolerable toxicity | 30 days after last dose | 60 days, 90 days after last dose | Every 2 months |
| Window period [1] | | | | | ± 3 days | ± 3 days | | | ± 5 days | ± 5 days | ± 5 days |
| Informed consent | X | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | |
| Demographics, past medical history [2] | X | | | | | | | | | | |
| Vital signs [3] | X | | | | X | | | X (every 2 cycles) | X | | |
| Physical examination [4] | X | | | | X | | | X (every 2 cycles) | X | | |
| BSA [5] | X | | | | | | | | | | |
| ECOG performance status [6] | X | | | | X | | | X (every 2 cycles) | X | | |
| Quality-of-life assessment [7] | X | | | | X (every 2 cycles) | | | | | | |

| Assessment/Time (21 days per cycle) | Screening Phase D-14~D-1 | Treatment Phase | | | | | | Monotherapy Maintenance Phase | Safety Follow-up | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 and Thereafter | | | | | | |
| | | D1 | D8 | D15 | D1 Once per cycle | D8 | D15 | One year after the initiation of treatment, or upon disease progression / intolerable toxicity | 30 days after last dose | 60 days, 90 days after last dose | Every 2 months |
| Adverse events [8] | X | X | | | X | X | | X (every 2 cycles) | X | X | |
| Concomitant medications [9] | X | X | | | X | X | | X (every 2 cycles) | X | X | |
| **Laboratory tests** | | | | | | | | | | | |
| Hematology [10] | X | | X | X | X | X | X | X (every 2 cycles) | X | | |
| Blood chemistry [11] | X | | X | X | X | X | | X (every 2 cycles) | X | | |
| Urinalysis [12] | X | | | | X (every 2 cycles) | | | X (every 2 cycles) | X | | |
| Stool routine [13] | X | | | | X | | | X (every 2 cycles) | X | | |
| 12-lead ECG [14] | X | | | | X | | | X (1 in 2 cycles) | X | | |
| Echocardiography [15] | X | | | | | | | | | | |
| Myocardial zymogram [16] | X | | | | | | | | | | |
| Hormone levels [17] | X | | | | X (every 2 | | | X (every 2 cycles) | X | | |

| **Assessment/Time (21 days per cycle)** | **Screening Phase D-14~D-1** | **Treatment Phase** | | | | | | **Monotherapy Maintenance Phase** | **Safety Follow-up** | | **Survival Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1** | | | **Cycle 2 and Thereafter** | | | | | | |
| | | **D1** | **D8** | **D15** | **D1 Once per cycle** | **D8** | **D15** | One year after the initiation of treatment, or upon disease progression / intolerable toxicity | 30 days after last dose | 60 days, 90 days after last dose | Every 2 months |
| | | | | | cycles) | | | | | | |
| Coagulation [18] | X | | | | X (every 2 cycles) | | | X (every 2 cycles) | X | | |
| Pregnancy test [19] | X | | | | | | | | | | |
| Infection indicators [20] | X | | | | X (every 2 cycles) | | | X (every 2 cycles) | | | |
| Virological testing [21] | X | | | | | | | | | | |
| **Dosing record** | | | | | | | | | | | |
| IE regimen in test group [22] | | D1-3 | | | D1-3 | | | | | | |
| IE regimen in control group [23] | | D1-5 | | | D1-5 | | | | | | |
| Apatinib [24] | | X | | | X | | | X | | | |
| **Efficacy** | | | | | | | | | | | |

| **Assessment/Time (21 days per cycle)** | **Screening Phase D-14~D-1** | **Treatment Phase** | | | | | | **Monotherapy Maintenance Phase** | **Safety Follow-up** | | **Survival Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1** | | | **Cycle 2 and Thereafter** | | | | | | |
| | | **D1** | **D8** | **D15** | **D1 Once per cycle** | **D8** | **D15** | One year after the initiation of treatment, or upon disease progression / intolerable toxicity | 30 days after last dose | 60 days, 90 days after last dose | Every 2 months |
| Tumor assessments [25] | X | | | | X (every 2 cycles) | | | X (every 2 cycles) | | | |
| Safety follow-up [26] | | | | | | | | X | X | X | |
| Subsequent treatments | | | | | | | | X | X | X | |
| Survival follow-up [27] | | | | | | | | X | | | X |

Note: In addition to the items and time points listed in the table, the investigator can add visits and other items as needed based on actual conditions.

1. Patients should sign the ICF within 14 days prior to dosing. The screening assessment should be completed within 14 days prior to dosing.

2. Demographics, past medical history, and treatment history should include date of birth, gender, ethnicity, cancer history (history of cancer diagnosis, surgery, radiotherapy, chemotherapy, etc.) and other comorbidities and their corresponding treatments. Among them, the cancer history should include time of initial diagnosis, pathological diagnosis, histological grading, clinical staging, etc.

3. Vital signs include pulse, respiratory rate, body temperature, and blood pressure. The vital signs measurement should be conducted within 7 days before the first dose, once every cycle, and on the Day

30 after the last dose, as well as once every 2 cycles during the monotherapy maintenance period.

4. Physical examination: A comprehensive physical examination (including body height, weight, general conditions, head and face, neck, chest, abdomen, perineum, limbs, and others) should be conducted within 7 days before the first dose, once every cycle, and on the Day 30 after the last dose. Body height only needs to be measured within 7 days before the first dose, while weight needs to be measured at every visit point. A targeted physical examination should be conducted in clinically indicated situations. Abnormal changes in physical examination results with clinical significance (including vital signs and ECOG performance status scores) should be recorded as AEs, and disease progression should not be reported as an AE. During the monotherapy maintenance period, physical examination should be conducted once every 2 cycles.

5. There is no need to recalculate BSA for each cycle, unless it is required by the study site guidelines or the subject's weight increases or decreases by more than 10% of the original weight. For obese subjects (body mass index > 30), the ideal weight should be used to calculate their BSA throughout the study.

6. ECOG score: The scoring should be conducted within 7 days before the first dose, once every cycle, and on the Day 30 after the last dose, as well as once every 2 cycles during the monotherapy maintenance period.

7. Quality-of-life assessment: The assessment should be conducted within 7 days before the first dose, once every 2 cycles, and on the Day 30 after the last dose. The score is calculated based on the responses to the "Quality-of-life Assessment" table.

8. Concurrent medications: The investigator should observe and record all concurrent medications/accompanying treatments from the signing of the ICF until the subject completes the safety follow-up and withdraws from the group. If the subject begins a new systemic anti-tumor treatment during the safety follow-up, only the concurrent medications/accompanying treatments of AEs related to the study drug should be recorded. During the survival follow-up, only whether other anti-tumor treatments are received should be recorded.

9. Adverse events: According to the terms and standards of NCI CTCAE V5.0, AEs will be recorded from the signing of the ICF until the end of the safety follow-up period. For specific AE collection period, please refer to Table 8.2 <AE/SAE Collection and Follow-up>. All AEs should be followed up until the end of the safety follow-up period or they have disappeared, recovered to baseline level or ≤

Grade 1, reached a stable state, or been reasonably explained (such as lost to follow-up, death). All AEs that occur from the signing of the ICF until the subject completes the safety follow-up and withdraws from the group should be observed and recorded, regardless of whether they are related to the study drug. All AEs will be recorded until they have completely disappeared or recovered to Grade 0 to 1, returned to baseline level, or reached a stable state. If the subject starts a new systemic anti-tumor treatment, only AEs related to the study drug should be recorded.

10. Hematology includes white blood cell count, neutrophil count/percentage, lymphocyte count, monocyte count, eosinophil count, basophil count, red blood cell count, haemoglobin, and platelet count. The determination should be conducted within 7 days before the first dose, once on D1, D8, and D15 of each cycle, and on the Day 30 after the last dose. Due to the risk of chemotherapy causing a decrease in neutrophil count, the investigator can add the corresponding test before chemotherapy based on the actual situation, and the occurrence of AEs need to be recorded. During the monotherapy maintenance period, the determination should be conducted once every 2 cycles.

11. Blood chemistry includes alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea, total protein (TP), albumin (ALB), creatinine (Cr), glucose (GLU), potassium ($K^+$), sodium ($Na^+$), calcium ($Ca2^+$), magnesium ($Mg^{2+}$), chloride ($Cl^-$), and endogenous creatinine clearance rate. The determination should be conducted within 7 days before the first dose, once on D1, D8, and D15 of each cycle, and Day 30 after the last dose, as well as once every 2 cycles during the monotherapy maintenance period.

12. Urinalysis includes white blood cells, red blood cells, glucose urine, and protein urine. If protein urine is ≥ 2＋, a 24-hour protein urine quantitative determination must be added. Urinalysis should be conducted within 7 days before the first dose, once every 2 cycles, and on the Day 30 after the last dose, as well as once every 2 cycles during the monotherapy maintenance period.

13. Stool routine: Stool routine should be conducted within 7 days before the first dose, once every cycle, and on the Day 30 after the last dose, as well as once every 2 cycles during the monotherapy maintenance period.

14. 12-Lead ECG: Attention should be paid to QT, QTcF, and P-R intervals. 12-Lead ECG should be performed within 7 days before the first dose, once every cycle, and on the Day 30 after the last dose.

QTcF can be calculated according to the formula QTcF=QT/(RR ^0.33). During the monotherapy maintenance period, 12-Lead ECG should be performed once every 2 cycles.

15. Echocardiogram: It should be conducted within 7 days prior to the first dose, and the investigator may increase the frequency if deemed necessary.

16. Myocardial zymogram includes lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), AST, and a-HBD. The determination should be conducted within 7 days prior to the first dose, and the investigator may increase the frequency if deemed necessary.

17. Hormone levels includes thyroid function and cortisol levels. The determination should be conducted within 7 days prior to the first dose and once every 2 cycles, and the investigator may increase the frequency if deemed necessary. During the monotherapy maintenance period, the determination should be conducted once every 2 cycles.

18. Coagulation function includes activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR). The determination should be conducted within 7 days before the first dose, once every 2 cycles, and on the Day 30 after the last dose, as well as once every 2 cycles during the monotherapy maintenance period.

19. Pregnancy test: Women of childbearing potential should undergo a serum pregnancy test within 72 hours before the first dose and on the Day 30 after the last dose.

20. Infection indicators include dynamic erythrocyte sedimentation rate (ESR, determined by the investigator based on necessity), C-reactive protein, and procalcitonin (the investigator may increase the frequency if deemed necessary). The determination should be conducted every two cycles, as well as once every two cycles during the monotherapy maintenance period.

21. Virological testing includes HBsAg (if positive, HBV DNA quantification determination is required), HCV-Ab (if positive, HCV-RNA quantification determination is required) and HIV-Ab. The testing should be performed within 28 days before the first dose.

22. IE regimen in test group: Ifosfamide 1.8 g/m$^2$/d + 500 ml of saline will be administered by intravenous infusion over 2 hours on Days 1-3 of each cycle, and mesna will be provided for rescue at 0 h, 4 h, and 8 h after ifosfamide infusion, while ensuring hydration. Etoposide 100 mg/m$^2$/d + 500/1000 ml of saline (ensuring that the concentration of etoposide does not exceed 0.25 mg/ml) will be administered by infusion lasting more than 30 minutes.

23. IE regimen in control group: Ifosfamide 1.8 g/m$^2$/d + 500 ml of saline will be administered by

intravenous infusion over 2 hours on Days 1-5 of each cycle, and mesna will be provided for rescue at 0 h, 4 h, and 8 h after ifosfamide infusion, while ensuring hydration. Etoposide 100 mg/m$^2$/d + 500/1000 ml of saline (ensuring that the concentration of etoposide does not exceed 0.25 mg/ml) will be administered by infusion lasting more than 30 minutes.

24. In the test group, apatinib tablets will be taken orally half an hour after meals, once a day, 500 mg each time, continuing until one year after enrollment, or until the occurrence of disease progression or unacceptable toxicity.

25. Tumor assessment: Radiological examination. The disease assessment should include enhanced CT or MRI of the primary neoplasm site (postoperative local plain film and local CT), chest CT plain scan, ECT whole body bone imaging or whole body PET/CT examination. The CT/MRI examination method and technique for the same subject must remain consistent throughout the study. Tumor assessment should be performed once every two cycles during the treatment phase of the study, once every three months for the first two years after the end of the treatment phase, and once every six months thereafter, until the end of the study or the death of the subject. The window period for radiological examination is allowed to be ±7 days. If disease progression is suspected (such as worsening symptoms), an unplanned radiological examination can be conducted.

26. Safety follow-up: Follow-up should be conducted on Days 30, 60 and 90 after the last dose. The first safety follow-up visit (Day 30) should be performed at the study site, including the assessments stipulated in the protocol; the second (Day 60) and third (Day 90) safety follow-up visits are telephone visits, only requiring the collection of new anti-tumor treatment, survival information, concurrent medications/accompanying treatments, and AEs.

27. Survival follow-up: After the safety follow-up period ends, the subject will enter the survival follow-up until the subject's death, loss to follow-up, withdrawal of consent, or discontinuation of the study by company. During this period, a visit will be conducted every 2 months via phone follow-up to collect survival information and subsequent treatment information (if the subject begains a new anti-tumor treatment, the treatment regimen and start and end times should be recorded).

### 4.6 Dosage and Administration

#### 4.6.1 Calculation of Body Surface Area

The dose of the study drug depends on the subject's BSA, which will be calculated based on the subject's

weight and body height before the first dose on the first day of the first month. Thereafter, it is not necessary to recalculate the BSA for each cycle, unless it is required by the study site or the subject's weight increases or decreases by more than 10%. For obese subjects (body mass index > 30), the ideal weight will be used to calculate their BSA throughout the study.

**4.6.2 Drug Regulations**

**4.6.2.1 Drug Preparation and Administration**

Apatinib: Administer orally 500 mg daily (single dose).

Ifosfamide: In the test group, ifosfamide 1.8 g/$m^2$/d + 500 ml of saline will be administered by intravenous infusion over 2 hours on Days 1-3 of each cycle, and mesna will be provided for rescue at 0 h, 4 h, and 8 h after ifosfamide infusion, while ensuring hydration. In the control group, ifosfamide will be administered on Days 1-5 of each cycle, with the same dosage and administration as the test group. Etoposide: In the test group, etoposide 100 mg/$m^2$/d + 500/1000 ml of saline (ensuring that the concentration of etoposide does not exceed 0.25 mg/ml) will be administered by infusion lasting more than 30 minutes. In the control group, etoposide will be administered on Days 1-5 of each cycle, with the same dosage and administration as the test group.

**4.6.2.2 Precautions for Drug Use**

Patients in the apatinib group need to measure their blood pressure twice daily, record the changes in blood pressure, and timely control blood pressure by medication.

The protein urine level should be rechecked every 2 cycles. If necessary, medication control should be given or the dose of apatinib should be reduced.

Reactions such as hand-foot rash should be monitored, hormones and topical antibiotics ointment can be given, and the dose of apatinib can be reduced if necessary.

Hematology should be monitored weekly after the completion of IE chemotherapy. Prophylactic use of colony-stimulating factors or pegylated colony-stimulating factors is required to prevent the occurrence of Grade IV or above myelosuppression.

**4.6.2.3 Unified Regulations for Drugs and Manufacturer**

Apatinib, 250 mg/tablet, manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Ifosfamide, 0.1 g/vial, manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Etoposide, 100 mg/vial, manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

**4.6.3 Criteria for Continuing Treatment**

Administration can be delayed for up to 2 weeks to allow for the recovery of laboratory toxicities or other non-hematologic drug-related effects. If toxicity has not recovered after a 2-week delay, the subject should discontinue the treatment. If it is determined that the subject can continue with the treatment, it may be necessary to reduce the dose of the study drug based on the minimum values in key analysis or toxicity effects, as detailed in the dose modification section.

Table 4.6.3.1 Criteria for Continuing Treatment

| **Variable** | **Day 1** |
|---|---|
| Platelets | $\geq 75\times10^9$/L |
| Neutrophils | $\geq 750\times10^9$/L |
| Bilirubin | ≤ 1.5 ×ULN |
| Transaminases | ≤ 2.5 × ULN |
| Other non-hematologic drug-related effects | Grade 1 or lower |

Although there is no haemoglobin standard for continuing treatment, subjects with anaemia should be closely monitored to ensure they do not have corresponding clinical symptoms.

In the same cycle, subjects with liver abnormalities including all the following conditions should discontinue treatment: bilirubin ≥ 2×ULN, transaminases (ALT or AST) ≥ 4×ULN; unless there is evidence indicating that the subject benefits (such as neoplasm reduction, disease stabilization) and the subject recovers within 3 weeks.

**4.6.4 Dose Modifications**

Table 4.6.4.1: Reduced Dose Levels

| **Dose Level** | Apatinib | Etoposide | Ifosfamide |
|---|---|---|---|
| Start level | 500 mg qd | 100 mg/m$^2$/d $d_{1-3}$ | 1.8 g/m$^2$/d $d_{1-3}$ |
| Level-1 | 250 mg qd | 50 mg/m$^2$/d $d_{1-3}$ | 1.5 g/m$^2$/d $d_{1-3}$ |
| Level-2 | 250 mg qod | 0 mg/m$^2$/d $d_{1-3}$ | 1.0 g/m$^2$/d $d_{1-3}$ |

For any subject who experiences Grade IV myelosuppression for more than 2 days, or delays chemotherapy for more than 7 days due to Grade 3-4 toxic side effects, or suspends targeted drug for more than 7 days, the treatment of the next cycle needs to be adjusted by reducing the dose. The reduced dose can be decreased no more than twice. If further dose reduction is needed, the subject should be temporarily withdrawn from the treatment until the subject's general condition recovers to the standard for continuing treatment (see 5.3). The dose suspension should not exceed 2 months, otherwise, the subject will be considered as withdrawn from the clinical study due to toxic side effects. The treatment will continue until disease progression or suspension for other reasons, such as unacceptable toxicity or withdrawal of consent.

**4.6.4.1 Dose Reduction Due to Hematologic Toxicity**

If a hematologic toxicity occurs in a subject in one group that meets the criteria listed in Table 4.6.4.1.1, the dose will be reduced in the manner specified in Table 5.4.1.

Table 4.6.4.1.1: Dose Reduction Criteria for Hematologic Toxicity

| **Worst Toxicity** | **Minimum Value** | **Dose Modification** |
|---|---|---|
| ANC | $< 1.0\times10^9$/L with infection/pyrexia, or<br>$< 0.5\times10^9$/L for more than 2 days | Reduced by 1 level [a, b] |
| Platelets | $< 25\times10^9$/L | Reduced by 1 level [a] |

[a] If the toxicity is experienced again, the dose will be reduced by two levels, until drug suspension.

[b] Support treatment with colony-stimulating factors may be used.

**4.6.4.2 Dose Reduction Due to Non-Hematologic Toxicity**

If a non-hematologic toxicity occurs in a subject in one group that meets the criteria listed in Table 4.6.4.2.1, the dose will be reduced in the manner specified in Table 5.4.1.

Table 4.6.4.2.1: Dose Reduction Criteria for Non-Hematologic Toxicity

| **Toxicity** | | **Worst Grade** | **Dose Modification** |
|---|---|---|---|
| Regardless of whether the treatment is sufficient, nausea or vomiting occurs. [a] | | ≥3 | Reduced by 1 level |
| Transaminases increased | Before the next dosing day or within 3 weeks after the next | ≥3 | Reduced by 1 level |

| | | | |
|---|---|---|---|
| | dosing day, it can be recovered to ≤ 2.5×ULN. | | |
| | Not recovered after 3 weeks of dose delay | ≥3 | If clinical benefit is demonstrated, the dose will be reduced by 1 level, otherwise, the study drug will be discontinued. |
| Alkaline phosphatase increased | Recovered to ≤ 2.5×ULN before the next dosing day or within 3 weeks after the next dosing day. | ≥3 | Reduced by 1 dose level |
| | Not recovered after three weeks | ≥3 | If clinical benefit is demonstrated, the dose will be reduced by 1 level, otherwise, the study drug will be discontinued. |
| Total bilirubin > ULN at any time | | ≥1 | Reduced by 1 level |
| Other | | ≥3 | Reduced by 1 level |

Before dose modification, all antiemetic treatment regimens should be applied, including 5-HT3 receptor antagonists/others/hexadecadrol.

**4.6.5 Dose-Limiting Toxicity**

Dose limiting toxicity (DLT) refers to any AE that meets the definition of DLT occurring within the first treatment cycle, but AEs clearly unrelated to the study drug should be excluded. DLT is defined as one or more of the following events:

(a) Absolute neutrophil count (ANC) < $0.5\times10^9$/L lasting for more than 7 days, or neutropenia accompanied by pyrexia (ANC < $0.5\times10^9$/L, and a single body temperature ≥ 38.5℃ or body temperature of 38℃ lasting for more than 2 days);

(b) Platelets < $25\times10^9$/L for more than 2 days;

(c) Grade 3 or 4 liver transaminase increased or Grade ≥2 bilirubin increased, and not returned to pretreatment levels (i.e., baseline levels) even 21 days after treatment;

(d) Non-hematologic toxicity of Grade 3 to 4 outside the liver (excluding nausea/vomiting that occurs without the implementation of an appropriate antiemetic regimen).

**4.7 Endpoints**

In this study, the primary endpoint is mPFS, which is used to evaluate whether the treatment with apatinib in combination with IE chemotherapy is superior to the IE chemotherapy alone in patients with relapsed or refractory osteosarcoma that progressed after first-line chemotherapy. Progression-free survival (PFS) refers to the time from the randomization to disease progression or any cause of death, evaluated by investigator based on RECIST v1.1, whichever occurs first.

Secondary endpoints included:

Overall survival (OS) refers to the time from the randomization to any cause of death.

Objective response rate (ORR) refers to the proportion of subjects whose best overall response (BOR) is CR or PR, evaluated by investigator based on RECIST v1.1.

Disease control rate (DCR) refers to the proportion of subjects whose best overall response (BOR) is complete response (CR), partial response (PR) and stable disease (SD), evaluated by investigator based on RECIST v1.1.

Duration of response (DoR) refers to the time from first unconfirmed complete response (CR)/ unconfirmed partial response (PR), evaluated by investigator based on RECIST v1.1, to progressive disease (PD) or any cause of death, whichever occurs first.

Time to response (TTR) refers to the the time from randomization to first CR/PR, evaluated by investigator based on RECIST v1.1.

Time to progress (TTP) refers to the time from randomization to progress disease, evaluated by nvestigator based on RECIST v1.1.

4-month PFS rate refers to the percentage of patients who were alive and free of disease progression at 4 months evaluated by investigator based on RECIST v1.1.

6-month PFS rate refers to the percentage of patients who were alive and free of disease progression at 6 months evaluated by investigator based on RECIST v1.1.

Exploratory endpoints included:

QoL is assesse using the EORTC QLQ-C30 questionnaire.

Event-free survival (EFS) refers to the time from randomization to the first occurrence of disease progression, recurrence, initiation of new anti-tumor therapy, or death from any cause, evaluated by investigator based on RECIST v1.1..

**4.8 Sample Size Calculation and Reasoning**

This study is a prospective, two-arm, multicenter, open-label clinical study. Currently, there is a lack of internationally recognized objective mPFS data for progressive relapsed or refractory osteosarcoma after traditional chemotherapy. The large difference in objective response rates after first-line chemotherapy and second-line chemotherapy makes it difficult to estimate the sample size for this study. However, based on the published retrospective data in the past three years by the Bone Neoplasm Department of Peking University People's Hospital and Peking University Shougang Hospital [17], we set the mPFS of 5 months (null hypothesis) obtained from the IE chemotherapy for progressive relapsed or refractory osteosarcoma as the underlying target, and expect to reach a mPFS of 11 months or higher (alternative hypothesis) as the target value. This study uses two-sided design, with $\alpha$=0.05 (two-sided), $\beta$=0.20 (power=80%), assuming that it will take 18 months to complete enrollment, with a follow-up period of 12 months. Patients will be enrolled at a 2:1 ratio with a dropout rate of 10%, the control group needs 26 patients, and the test group needs 52, with a total of 78 patients.

**4.9 Study Progress**

From August 2021 to March 2022, complete the Ethics Committee (EC) review and initiate the study.

From April 2022 to December 2022, complete the enrollment of 39 subjects in the first phase and conduct follow-up.

From January 2023 to September 2023, complete the enrollment of 39 subjects in the second phase and write an interim follow-up report.

From October 2023 to September 2024, conduct follow-up in the second phase, conduct data analysis, and summarize conclusions.

**5. Study Site and Data Management**

**5.1 Regulatory Documents**

**5.1.1 Regulatory Approval/Notification**

This study protocol and any amendments must be submitted to the relevant national regulatory authority (if applicable). The study can only be initiated after all local regulatory requirements are met.

**5.1.2 Preparation of Required Documents Prior to the Clinical Study**

Before the start of the clinical study, the study site must provide the following documents:

The protocol and amendments (if any) signed and dated by the principal investigator.

Copies of the written approval letters signed and dated by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for the study protocol, amendments, ICF, any recruitment materials, and subject compensation plan (if applicable). The approval letters must clearly specify the specific protocol information through the title and number, and must be signed by the chairperson or authorized person.

**5.2 Subject Identification Information, Enrollment and Screening Log**

The investigator agrees to complete the subject qualification and screening log in order to identify each subject's identification during and after the study. CRA will review the integrity of this document.

The subject qualification and screening log will be considered confidential and will be kept in the study files by the investigator. In order to ensure the privacy of subjects, no photocopies will be made. In all reports and communications related to the study, subjects will be identified by the assigned codes.

The investigator must also complete the subject screening log, which reports the circumstances under which the investigator meets the subjects and determines they are eligible for enrollment in the study.

**5.3 Source Documents**

To verify the data collected in the CRF, the following source data must be available at a minimum: subject's identification information, eligibility, and study information; dates of study discussions and informed consent; visit dates; results of safety and efficacy parameters required by the study protocol; all AEs and follow-up records of AEs; concurrent medications; records of drug receipt/distribution/return; study drug administration information; date of study completion and reasons for early discontinuation of the study drug or withdrawal from the study (if applicable).

In addition, the investigators who are able to complete the source documents should be clearly defined.

The type and level of detail of subject's source data should at least be consistent with the routine records of the study site for standard medical care. Prior to the start of the study, the investigator will review specific detail requirements and describe them in the monitoring guidelines (or other similar documents).

**5.4 Completion of Case Report Form**

The CRF of each subject will be provided in electronic format.

This study will adopt the method of Electronic Data Capture (EDC). The study data will be transcribed from the source documents to an electronic document by the investigator, and this electronic document will be

regarded as the CRF.

It should be ensured that all subjective measurement indicators recorded in the CRF are completed by the same person who complete the baseline form. The investigator must verify that all data entered into the CRF are accurate and correct.

All CRF records, corrections, and modifications must be completed by the investigator or other authorized study personnel. When necessary, EDC will generate queries. The investigator or authorized study personnel must review the CRF (if applicable) and resolve the queries.

**5.5 Data Quality Assurance/Quality Control**

Measures must be taken to ensure the accuracy and reliability of the data. Specific measures include selecting qualified investigators and appropriate study sites, and having investigators and relevant personnel discuss the specific process of the study protocol before the implementation of the study. Written instructions will be provided regarding sample collection, preparation, and transportation. A guideline will be provided for completion of the CRF, and it will be reviewed jointly with investigators before the start of the study. During on-site monitoring, CRA will review the accuracy and completeness of the CRF, and any deviations found during the review process will be resolved with investigators or their designated staff. After the data are uploaded to the clinical study database, the accuracy and consistency with the source data will be checked.

The specific requirements are as follows:

The study personnel must be physicians who have undergone clinical study training and work under the guidance of senior professionals.

Before the start of the clinical study, an investigation must be conducted to ensure that the clinical wards meet standardized requirements and that necessary resuscitation equipment is available.

Study drugs should be administered to subjects by professional nursing staff, who thoroughly understand the drug usage, ensuring the subjects' compliance.

The study site must strictly follow the study protocol and truthfully complete the case observation form.

CRA should follow the operating procedures, supervise the progress of the clinical study, and ensure that all data records and reports are correct and complete, all CRFs are completed correctly and are consistent with the source data, and the study is conducted according to the clinical study protocol.

Investigators should ensure that they can be contacted at any time via telephone, fax, or email.

Once a serious adverse event (SAE) occurs, the CRA must promptly notify the study site, and if necessary, the study may be temporarily suspended.

All sites participating in this study should accept the audit from the sponsor and the drug regulatory authority. It is particularly important that the investigators and related personnel should provide convenience and time for monitoring and auditing.

**5.6 Record Retention**

In accordance with the requirements of the ICH/GCP guidelines, the investigator/study site will preserve all CRFs and all source records supporting the data collected from each subject, as well as all study documents stipulated in Section 8 of the ICH/GCP (Documents Necessary for Conducting Clinical Studies) and all study documents required in relevant regulations. The investigator/study site will take appropriate measures to prevent these documents from being accidentally or prematurely destroyed.

The essential documents of the clinical study must be retained for at least 2 years after the formal cessation of the clinical study. When these documents are no longer required to be kept, the collaborative group has an obligation to notify the investigator/study site.

If the investigator responsible for this matter retires, changes practice location, or is no longer responsible for keeping these study records for other reasons, the task of keeping these records must be transferred to personnel willing to take on this responsibility. At the same time, the name and address of the new custodian must be notified to the collaborative group in writing. Before obtaining the written approval of the collaborative group, the investigator should not transfer or dispose of any study document under any circumstances.

If the relevant regulatory authority needs to review any records related to this study, the investigator must allow them access to these documents.

**6. Statistical Analysis Methods**

Full analysis set (FAS): In accordance with the intention-to-treat (ITT) principle, efficacy analysis will be conducted on all subjects who have received at least one dose of study drug.

Per-protocol set (PPS): Refers to the set of subjects who comply with the study protocol, have good compliance, and have completed all required procedures. This dataset does not include subjects who violate the study protocol, such as those do not receive the prescribed treatment dose, those have missing major variables, or those use explicitly prohibited drugs.

Safety set (SS): Refers to the set of subjects who have used the prescribed drug once or more after screening, regardless of whether they are included in the PPS. All AEs and adverse reactions should be analyzed in the

SS. Subjects who have not taken any study drug or have no follow-up observation data after enrollment will be excluded from the set. All statistical calculations will be performed using SAS Statistics (Version 9.4) and GraphPad Prism (Version 5.0) statistical analysis system programming.

Statistical description: All indicators will be described according to their nature. Qualitative indicators will be represented by the frequency and percentage of given categories; quantitative indicators will be represented by the number, mean, standard deviation, median, minimum, and maximum. The results will be mainly expressed using statistical tables with groups as the vertical column head, or statistical figures will be used to present the results when necessary.

Statistical inference: The efficacy evaluation will be based on the analysis of FAS and PPS, while the safety evaluation will be based on the analysis of SAS. Survival analysis will be conducted using the Kaplan-Meier method, with the Kaplan-Meier curve plotted and a 95% confidence interval reported. The intergroup comparison of PFS will use the Cox proportional hazard model. The paired t-test will be used for intragroup comparisons of measurement data, while the grouped t-test will be used for intergroup comparisons. The chi-square test will be used for intergroup comparisons of count data, and the Pearson analysis will be used for correlation analysis of two continuous variables, with the Fisher's exact probability method used when necessary.

## 7. Safety Evaluation

### 7.1 Drug Risks

This drug involves systemic application to kill neoplasm cells or inhibit their proliferation. It is one of the methods for comprehensive treatment of malignant neoplasms. For some patients, it can prolong survival time and improve quality-of-life. However, not all neoplasms are sensitive to this drug. While the drug kills neoplasm cells, it also has certain toxicity to normal human tissues and organs. Therefore, the drug used in this study carries certain risks and adverse reactions. The main risks and adverse reactions include but are not limited to the following:

1. Drug allergy, which can lead to anaphylactic shock if serious;
2. Myelosuppression, with a decrease in white blood cells, red blood cells, and platelets, leading to severe infections, serious bleeding, and other life-threatening conditions.
3. Gastrointestinal reactions, including nausea, vomiting, and loss of appetite, which can lead to gastrointestinal haemorrhage if serious.

4. Mucositis, mouth ulceration, diarrhoea, etc., which can lead to dehydration if serious.
5. Hepatic impairment;
6. Hypertension;
7. Proteinuria, renal impairment;
8. Heart or lung function impairment, which can lead to pulmonary fibrosis, lung function impairment, and respiratory failure, as well as arrhythmia, myocardial ischaemia, myocardial infarction, and cardiac failure if serious.
9. Drug solution leakage and phlebitis;
10. Hand-foot syndrome, alopecia, etc.;
11. Systemic or local pigmentation;
12. Symptoms of the central nervous system and other toxic side effects;

During chemotherapy, the treatment may be discontinud due to severe reactions or other reasons. If the chemotherapy is ineffective, or disease progression occurs, or there is drug resistance to the chemotherapy, it may be necessary to change the treatment regimen.

**7.2 Definition and Classification of Adverse Events**

An AE refers to any unfavorable event experienced by subjects in clinical study who have received a study drug (either investigational or non-investigational). Therefore, an AE can be any unfavorable and unexpected sign (including abnormal findings), symptom, or disease that has a temporal relationship with use of study drug (either investigational or non-investigational), regardless of whether it is indeed related to the drug (as defined by the International Committee on Harmonisation (ICH)).

An AE may be any newly occurring event or event that has worsened in severity and frequency from baseline, including abnormal laboratory results and abnormal results of other diagnostic methods.

The AE evaluation includes type, incidence, severity (graded according to NCI CTCAE version 5.0, start and end times, SAE or not, causality, and outcome.

During the study, AEs, including signs and symptoms during the screening phase, will be recorded on the AE page of the CRF. Note: The investigator will begin collecting AEs from the time the subject signs the ICF.

**Serious Adverse Events**

According to the definition of ICH, any AE that occurs at any dose and has the following characteristics should be considered as an SAE:

1. Leading to death;

2. Life threatening (the subject is at risk of death at the time of the event; this does not include an event that, if it gets more serious, could theoretically lead to death);

3. Leading to severe irreversible symptoms, requiring immediate emergency hospitalisation.

4. Leading to persistent or significant disability/incapacity;

5. Important medical events *

*: Certain important medical events, although not immediately life-threatening, leading to death or hospitalization, may harm the subject's health or require treatment intervention to prevent the occurrence of one of the results listed in the above definition. These situations, judged by the investigator as potentially leading to serious clinical consequences, are referred to as important medical events. The determination of important medical events is based on the investigator's medical knowledge and clinical experience. A rapid reporting procedure must also be adopted for important medical events.

Unlisted (Unexpected) Adverse Event/Safety Reference Information

Unlisted AEs refer to AEs that are inconsistent with the applicable drug safety reference information in terms of nature and severity. For the study drug, the expectedness of an AE is determined by whether the event is listed in the Investigator's Brochure.

**7.3 Definition of Causality**

Not related: The AE is not related to the study drug.

Unlikely related: The AE is more related to other circumstances, such as concurrent medications and comorbidities, or is considered unrelated to the study drug in terms of the timing of occurrence.

Possibly related: The AE may be related to the study drug, other circumstances such as concurrent medications and comorbidities cannot fully explain it; or the causality cannot be ruled out in terms of the timing of occurrence.

Probably related: The AE may be caused by the study drug, suggested by the temporal relationship, and the possibility of other explanations is very small.

Related: The AE has been listed as a possible adverse reaction, and there are no other reasons to explain it. The temporal relationship suggests a very strong correlation (confirmed by dechallenge and rechallenge).

**7.4 Reporting Procedures**

**7.4.1 All Adverse Events**

All AEs, regardless of whether they are serious, need to be reported from the time the subject signs ICF until the subject completes the last study-related procedure (including follow-up visits).

All events that meet the criteria of SAEs should be reported according to the SAE process, regardless of whether they belong to the specific evaluation in the study protocol.

All AEs, regardless of whether they are serious, severity, or the causal relationship with the study treatment, must be recorded in medical terms on source documents and CRFs. At any time, if a symptom and a sign can be attributed to a common cause, a diagnosis of the disease should be given as much as possible (for example: cough, rhinorrhoea, sneezing, sore throat, and hyperaemia should be reported as "upper respiratory tract infection"). The investigator must make a judgment on the causal relationship between the AE and the study drug and record the causal relationship on the CRF. All measures taken against AEs should be recorded in the source medical records.

The study site is responsible for promptly reporting AEs to the regulatory authority. The company also needs to report all unlisted (unexpected) SAEs related to study drug to the investigator. The investigator must report these events to the relevant IEC/IRB that approved the study protocol, unless the EC has special requirements, and in this case, the IEC/IRB needs to make relevant records.

**7.4.2 Serious Adverse Events**

For all SAEs that occur during the clinical study, the investigator must report them to the study lead within 24 hours of awareness.

The details of SAEs should be filled in the SAE form, and the form should be faxed to the study lead. The report must be signed by at least one investigator and sent to the study lead within 24 hours. Both the initial and follow-up reports of SAEs should be sent via fax.

For all SAEs that have not recovered by the end of the study, or have not recovered after the subject's discontinuation of the study, follow-up must be conducted until one of the following results is experienced:

1. The event is resolved;
2. The event is stable;
3. The event returns to the baseline level (if the baseline level/status is known);
4. The event can be attributed to other drugs besides the study drug or other factors unrelated to the execution of the study.
5. It is unlikely to obtain any additional information (the subject or doctor refuses to provide more information, or the subject is still lost to follow-up after various attempts).

In a clinical study, if a subject dies for any reason, it will be considered an SAE. However, some events that require hospitalization or prolonged hospitalization may not be reported as SAEs. Such situations include:

1. Hospitalization due to social reasons, not due to AEs.

2. Hospitalization for surgery or other treatments or examinations which have been pre-scheduled prior to entering the study (must be recorded in the eCRF).

Regarding the reporting of AEs, there may be other special requirements (such as those from the EC), but the above requirements must also be met.

**7.4.3 Pregnancy**

If the investigator discovers that a subject is pregnant during the course of the study, a pregnancy report form must be completed and all initial reports of the pregnancy must be reported to the company within 24 hours of becoming aware. Any subject who becomes pregnant during the study must immediately withdraw from the study and stop further study treatment.

If a subject becomes pregnant during the study, the investigator should obtain a written medical information disclosure authorization. The investigator then will contact her obstetrician and gynecologist, and complete the pregnancy notification form.

For subjects who become pregnant in the study, the investigator should follow up on the outcome of the pregnancy and the condition of the fetus.

## 8. Subject Protection

### 8.1 Investigator Responsibilities

The investigator is responsible for ensuring that the implementation of the clinical study complies with the study protocol, current guidelines of the ICH Good Clinical Practice (GCP), and applicable regulations.

GCP is the international ethical and scientific specification for the design, implementation, recording, and reporting of studies involving human subjects. Adherence to this specification is to protect the rights, safety, and health of the subjects in the study, to be in line with the Declaration of Helsinki, and to ensure the credibility of the data from the clinical study.

### 8.2 Independent Ethics Committee or Institutional Review Board

Before the study begins, the investigator will provide the IEC/IRB with the latest versions and complete photocopies of the following documents:

The final version of the study protocol and applicable amendments;

The ICF (and any other written materials provided to the subjects);

Investigator's Brochure (or similar information) and amendments/supplementary documents;

Subject recruitment materials;

Information on providing compensation for damages related to the study or remuneration to subjects participating in the study;

Investigator's curriculum vitae or equivalent information (such as proof provided by IEC/IRB, not essential);

Information about funding, the name of the company, the affiliation of the site, other potential conflicts of interest, and incentives on the subjects;

Any other documents required by the IEC/IRB to fulfill its responsibilities.

The study will only be implemented after the IEC/IRB has fully approved the final protocol, amendments (if any), ICF, applicable recruitment materials, and subject compensation plan, and the company has received a copy of the approval letter. This approval letter must indicate the date and must clearly specify the IEC/IRB and the approved documents.

During the study, where applicable, the investigator will submit the following documents and their updates to the IEC/IRB for their review and approval:

Study protocol amendment;

Revision of the ICF and any other written materials provided to the subject;

New or revised subject recruitment materials (if applicable);

Revised information on compensation for damages related to the study or remuneration to subjects participating in the study (if applicable);

The new version of the Investigator's Brochure and its amendments/supplementary documents;

A summary of the study status (submitted in accordance with the time specified in the IEC/IRB guidelines, at least once a year);

Reports of serious, unlisted/unexpected, and study drug-related Aes;

New information that may have a negative impact on the safety of subjects or the implementation of the study;

Protocol deviations or changes for the elimination of urgent harm to subjects;

Report of subject's death under the care of the investigator;

Notification of new investigator responsible for this study;

Any other requirements of the IEC/IRB.

All amendments to the study protocol (except for purely administrative revisions that have no impact on the subjects, data, or implementation of the study), amendments and applicable versions of the ICF, must be

promptly submitted to the IEC/IRB for review and approval before any changes are made.

Re-approval should be accompanied by written proof (except for purely administrative revisions that have no impact on the subjects, data, or implementation of the study).

At the end of the study, the investigator (or the company, if required) will notify the IEC/IRB of the end of the study.

**8.3 Informed Consent**

In accordance with local regulations, each subject (or his/her legal representative) must give written consent after fully understanding the nature of the study. This written consent must be signed before any study-related procedures are implemented. The ICF used must be reviewed and approved by the collaborative group and the IEC/IRB, and written in a language that the subjects can read and understand. The ICF should comply with the Declaration of Helsinki, current ICH and GCP guidelines, relevant regulations, and company policies.

Before subjects enter this study, the investigator or authorized study personnel must explain to the subjects or their legal representative the purposes, methods, possible benefits, and potential risks of the study, as well as any possible discomforts. Subjects should be informed that participation in the study is voluntary and they can withdraw at any time. The choice to participate in the study or not will not affect their disease treatment in any way. Finally, subjects will be aware that the investigator will retain a copy of their identity registration form for long-term follow-up when necessary. Health authorities and authorized company staff may access their medical records within the scope permitted by law or regulation, but their privacy will not be invaded. By signing the ICF, subjects authorize such access and agrees that their doctor may contact them again when necessary to obtain a consent form for further safety evaluation, or to obtain information about their survival status when needed.

Subjects or their legal representative should have ample time to read the ICF and ask questions. After the investigator's explanation and before the subjects' enrollment, subjects or their legal representative should sign their name and date on the ICF for record. After signing the ICF, subjects should receive a copy of the ICF.

If a subject or his/her legal representative cannot read and write, a fair witness should be involved in the entire informed consent process (including reading and interpreting all written information), and sign his/her name and date personally after the subject or legal representative gives verbal consent.

**8.4 Confidentiality of Personal Data**

The personal data collected and processed from the subjects participating in this study will be limited to the

data necessary to complete the purpose of this study.

When collecting and utilizing this data, sufficient preventive measures must be taken to ensure confidentiality and compliance with laws and regulations on privacy protection. Appropriate technical and organizational measures must be taken to protect personal data from unauthorized disclosure or access, accidental or illegal destruction, or accidental loss or alteration. Collaborative group staff who will access the subjects' personal data must ensure the confidentiality of the subject information.

Before collecting personal data, the investigator will obtain the consent of subjects (or their legal representative). The content of this consent form should include the authority to transmit data to other institutions and countries.

Subjects have the right to obtain personal information through the investigator and can request to correct any errors or incomplete data. Appropriate responses should be given to such requests based on the content and purpose, the status of the study, and relevant laws and regulations.

## 9. Study Management

### 9.1 Protocol Amendment

In the absence of a formal amendment proposed by the study site, no investigator can modify this protocol. All protocol amendments must be issued by the study lead and signed and dated by the investigator. A protocol amendment should not be implemented without prior approval from the IEC/IRB, or when objections are raised by the relevant regulatory authority, unless it is necessary to alleviate immediate harm to subjects, in which case the amendment must be immediately submitted to the IEC/IRB and relevant regulatory authority later. The approval letter of amendments reviewed by the investigator and IEC/IRB must be provided to the collaborative group or its designated person. If these amendments only involve the logistics or management of this study, it is only necessary to notify the IRB (and IEC, if required).

During the course of the study, protocol deviations are inevitable. The investigator or other participating physicians should contact the collaborative group for protocol deviations. In any case, they should contact with the collaborative group as soon as possible, to discuss the details, and reach a consensus on the appropriate subsequent handling. Any protocol deviation should be recorded in the CRF and source documents, and the deviation and its reason should be described in the source documents.

### 9.2 Study Completion/Discontinuation

#### 9.2.1 Study Completion

This study will be considered completed when the last visit of the last subject is completed. When all visits

of the last subject at the study site are completed, the final data of the study site will be locked within the time specified in the clinical study protocol.

**9.2.2 Study Discontinuation**

If there is a reasonable cause, and sufficient communication has been made before the planned discontinuation, the investigator can initiate the site closure at any time.

The reasons for the investigator to close the study site in advance include but are not limited to:

The investigator does not comply with the study protocol, IEC/IRB requirements, local health authority's regulations, company procedures, or GCP guidelines;

The number of subjects recruited in the study is insufficient;

Further development of the drug is discontinued.

After the clinical cut-off date, the following data will be collected from subjects who are still receiving treatment with the study drug:

Study drug administration;

AEs occurring in the subject during the treatment phase or within 30 days after the last dose of the study drug;

The concomitant drug therapies used when an SAE occurs, as well as the drug therapies used for the treatment of these SAEs;

Values indicating the onset of AEs or the severity of toxicity changing to a lower or higher level, the most abnormal values observed in AEs, and the laboratory values when AEs are resolved.

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