A Phase 1 Study of HLX06, a Humanized Monoclonal Antibody Targeting Human Vascular Endothelial Growth Factor Receptor-2 in Patients with Advanced Solid Tumors Refractory to Standard Therapy

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Statement of Compliance

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidentiality. This documentation includes the study protocol, Investigator's Brochure, electronic data capture (EDC) system, and other scientific data.

This study will not be conducted without the prior written approval of a properly constituted Investigational Review Board (IRB) or Independent Ethics Committee (IEC).

No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Investigator: _____ Name of Site: _____

(Printed name)

Signature: _____ Date: _____

(YYYY-MMM-DD)

List of Abbreviations and Definition of Terms

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil counts
aPTT	Activated Partial prothrombin time
AST	Aspartate aminotransferase
ATD	Accelerated titration design
AUC	Area under curve
BOIN	Bayesian optimal interval design
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CEA	Carcinoma embryonic antigen
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCP	Good clinical practice
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B “e” antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCG	Human chorionic gonadotropin
Hct	Hematocrit
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IC50	50% inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IV	Intravenous
KDR	Kinase domain receptor
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PO	Per OS
PR	Partial response
PS	Performance status
Q3W	Every three weeks
QD	Once every day
QOL	Quality of Life

QW	Once every week
RBC	Red blood cells
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
TSH	Thyroid-stimulating hormone
ULN	upper limit of normal values
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
WBC	White blood cell (counts)
WHODD	World Health Organization Drug Dictionary
WWCBP	Women with child bearing potential

SYNOPSIS OF THE STUDY

Title

A Phase 1 Study of HLX06, a Humanized Monoclonal Antibody Targeting Human Vascular Endothelial Growth Factor Receptor-2 in Patients with Advanced Solid Tumors Refractory to Standard Therapy.

Sponsor

Henlix Biotech Co. LTD

Investigational product

HLX06 recombinant anti-vascular endothelial growth factor receptor 2 (VEGFR2) human IgG_1 monoclonal antibody.

Study type

Interventional

Study phase

Phase 1 first-in-human study.

Primary objective

To identify safety and the maximum tolerated dose (MTD) of HLX06 in patients with advanced or metastatic tumors refractory to standard therapy.

Secondary objectives

- The pharmacokinetics of HLX06 at different doses in patients.
- The pharmacodynamics of HLX06 at different doses in patients.
- The immunogenicity of HLX06 in human beings.
- The anti-tumor effects of HLX06 in patients.
- The potential prognostic and predictive biomarkers of HLX06 for advanced solid tumors.

Primary outcome measures

- Numbers and percentage of patients with adverse events (AEs).
- Maximum tolerated dose of HLX06.

Secondary outcome measures

- Maximum concentration (C_{max}) in different cohorts.
- Minimum concentration (C_{min}) in different cohorts.
- Area under concentration (AUC_{0-tau}) in different cohorts.
- Half-life ($T_{1/2}$) of HLX06 in different cohorts.
- Clearance (CL) rate of HLX06 in different cohorts.
- Volume of distribution (V_{ss}) at steady state in different cohorts.
- The presence and percentage of anti-HLX06 antibody (immunogenicity).
- Disease control rate.
- Overall response rate.
- Duration of response

Eligibility criteria

Inclusion criteria

- Eligible patients must be 18-years of age or older or per local regulations.
- Patients with histologically-proven measurable or evaluable advanced or metastatic solid tumors who have failed standard therapy or for whom no standard therapy is available. (For patients with hepatocellular carcinoma, the diagnosis needs to be supported by dynamic CT/MRI, if pathological confirmation is not attainable)
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 at the time of study entry.
- Able to provide informed consent.
- A life expectancy longer than three months.
- Adequate hematologic functions, as defined by: absolute neutrophil counts ≥ 1500/mm^3; a hemoglobin level ≥ 10 gm/dL; a platelet count ≥ 100,000/mm^3.
- Adequate hepatic function defined by: a total bilirubin level ≤ 1.5x of upper limit of normal (ULN); aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤ 2.5 x of ULN or ≤ 5x of ULN in known hepatic metastases or with primary hepatocellular carcinoma.
- Adequate renal function, as defined by the creatinine clearance rate ≥ 50 mL/minute by Cockcroft-Gault formula.
- Adequate cardiac function defined as left ventricular ejection fraction (LVEF)≥ 50%.
- Use of effective contraceptive measures if procreative potential exists.

- At least 28 days from prior major surgery, prior cytotoxic chemotherapy, or prior therapy with investigational agents (or medical device) or local radiotherapy before 1st infusion of HLX06.
- For patients with hepatocellular carcinoma, their Child-Pugh score has to be A.
- Able to be followed up as required by the study protocol.

Exclusion criteria

- Patients with large centrally located pulmonary lesions adjacent to or invading large blood vessels.
- Hemoptysis more than ½ teaspoon (approximately 2-3 mL) of red blood per day.
- Patients who still have ≥ grade 2 toxicities from prior therapies.
- Concurrent unstable or uncontrolled medical conditions with either of the followings:
    - Active systemic infections;
    - Poorly controlled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥100 mmHg), or poor compliance with anti-hypertensive agents;
    - Clinically significant arrhythmia, unstable angina pectoris, congestive heart failure (class III or IV of New York Heart Association [NYHA]) or acute myocardial infarction within 6 months;
    - Uncontrolled diabetes or poor compliance with hypoglycemics;
    - The presence of chronically unhealed wound or ulcers
    - Other chronic diseases, which, in the opinion of the investigator, could compromise safety of the patient or the integrity of study.
- Newly-diagnosed or symptomatic brain metastases (patients with a history of brain metastases must have received definitive surgery or radiotherapy, be clinically stable, and not taking steroids for brain edema). Anticonvulsants are allowed.
- Any concurrent malignancy other than basal cell carcinoma or carcinoma in situ of the cervix. (Patients with a previous malignancy but without evidence of disease for ≥ 3 years are allowed to participate).
- Pregnancy (confirmed by serum beta human chorionic gonadotropin [ßHCG]) or breast-feeding (for female patients only).
- A known history or clinical evidence of a deep vein or arterial thrombosis, or pulmonary embolism within 6 months of first infusion of HLX06.
- Less than six weeks from last infusion of ramucirumab, or any other anti-VEGF monoclonal antibody therapy (Last treatment with other monoclonal antibodies targeting

proteins other than anti-angiogenic factors is permitted if ≥ 4 weeks prior to the first infusion of HLX06).

- Proteinuria ≥ 2+ in routine urinalysis (patients with a protein value of ≤500 mg confirmed by a 24-hour urine collection are eligible).
- Known history of human immunodeficiency virus infection (HIV).
- The patient is the investigator, sub-investigator or any one directly involved in the conduct of the study.

Study design

This study employs the modified accelerated titration design (ATD) 2A[1] and Bayesian optimal interval design (BOIN) to assign patients in the study cohort and identify MTD.

ATD 2A design assumes that the toxicities and effects increase monotonically with doses. It starts with a rapid initial escalation phase by using cohorts of a single new patient to lower the probability of exposing patients to sub-therapeutic doses.[1] When moderate-to-severe toxicities emerge at higher doses, the acceleration phase ends and the study returns to cohorts with 3 new patients.

The BOIN design is a novel adaptive dose-finding method that allows dose escalation and de-escalation and estimates the posterior probability of toxicity rate using updated information [2]. This design is considered to have higher probability of identifying the MTD.

Dose levels and sample size: 250, 500, 750, 900, 1200, 1500 mg (flat dose, with no adjustment of body weight or body surface area)[3]. A maximum of 30 patients will be enrolled in the phase 1 study. Patients who withdraw from the study during the first cycle due to reasons not related to treatment-emergent toxicities will be replaced.

Dose escalation sequence is modified from the Fibonacci sequence.

Determination of starting dose and its dose levels: the starting dose is **500** mg (flat dose), which is at dose level 2 and approximately equal to 1/6 of human equivalent dose of highest non-severely toxic dose (HNSTD) in the *cynomolgus* study[4].

Target toxicity rate: 30%

Study cycle: Every four weeks.

ATD phase and cohort size

The accelerated phase starts with one new patient per cohort. When the patient does not experience dose-limiting toxicities (defined later) during the first cycle of treatment at the assigned dose level, the next new patient will be assigned to the next higher dose level of HLX06 *(ie. intrapatient dose escalation is NOT allowed).*

When the first instance of first-cycle dose-limiting toxicities (DLTs), or the second instance of first-cycle grade≥2 toxicities of any types occurs, the acceleration phase stops and the cohort expands to **three** new patients at the current and subsequent dose levels and switch to BOIN design.

Dose escalation/de-escalation rule and Bayesian optimal interval design (BOIN)
After the end of acceleration phase, the decision to escalate or de-escalate in subsequent cohorts is based on the numbers of patients experiencing DLTs and the total number of patients treated at the current dose level (Table 1)**.** The decision to escalate or de-escalate is based by pre-defined safety and toxicity boundary. If the probability of the DLT rate falls below the safety boundary, the dose for the next cohort escalates. By contrast, if the probability of DLTs arises above the toxicity boundary, the dose de-escalates in the next cohort. Otherwise, the dose level stays the same in the next cohort. The enrollment continues until the maximum of 30 patients is reached. The safety boundary in this study is set at 21% (70% of target rate); and the toxicity boundary, at 39%, (130% of target rate), respectively. The detailed rules are described on page 19 . A hypothetical scheme of ATD and BOIN design in the 30 patients is shown in Figure 1.[2]

Rules of early stop

This study also employs two rules for early stopping of the study.

1. Stop the trial if the lowest dose (250 mg) is eliminated due to overt toxicities.
2. Stop the trial and estimate the MTD if the number of new patients treated at the current dose level reaches 15.

Determination of MTD

After the trial is completed, we determine the MTD based on the isotonic regression as specified in Yuan et al[5]. The determined MTD is the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate of 30%. If there are ties, we select the higher dose level when the isotonic estimate is lower than the target toxicity rate; and we select the lower dose level when the isotonic estimate is greater than the target toxicity rate.

The parameters of BOIN design, operating characteristics and sensitivity analysis are described in the protocol.

Definition of DLTs

DLTs are side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment during the **first cycle (first 4 weeks)** of treatment.

Common Toxicity Criteria for Adverse Events (CTCAE) 4.0 are used for grading of toxicities in this study.

The definitions of DLT include:

- Grade-4 nonhematologic toxicities;
- Grade≥3 febrile neutropenia;
- Any grade-3 non-hematologic toxicities lasting more than 3 days despite of optimal supportive care;
- Grade-3 nonhematologic laboratory abnormalities that persist more than one week and require medical intervention or hospitalization;
- Grade-4 thrombocytopenia requiring platelet transfusion or leading to life-threatening bleeding event.
- Grade-4 neutropenia > 7 days.

Treatment cycle and route of administration:

Each cycle consists of 4 weekly intravenous infusions at the assigned dose level.

Patients with good tolerability and disease control will continue treatment until disease progression or up to the maximum of one year, withdrawal from study or death, whichever comes first. If the individual patient still benefits from the Investigational Product after one year of treatment, extending the treatment beyond one year may be arranged with the Sponsor.

Pre-medications

Primary prophylaxis for first infusion reaction of HLX06 is NOT mandatory. If the patients experience infusion reactions, allergic reactions, nausea, vomiting or other symptoms/signs related to infusion of experimental drugs, pre-medications to mitigate these reactions with antihistamine, acetaminophen, corticosteroid or 5-HT3 antagonist or by institutional guidelines are permitted in subsequent infusions. Infusion time is two hours.

Treatment evaluation

RECIST criteria 1.1 will be used for treatment evaluation[1].

1. For the first 24 weeks, treatment evaluation is conducted every 8 weeks (i.e. every 2 cycles) despite treatment delay.
2. After 24 weeks, treatment evaluation is conducted every 12 weeks (3 cycles).

Dose modification scheme

Dose modification is based on the toxicities from previous infusions. Patients who experience reversible DLTs **are** allowed to receive additional infusions at the next lower dose level, provided that the toxicities have reverted to grade≤1 in 28 days after last infusion, and that the patients still meet the inclusion criteria for adequate organ functions.

For patients who experience DLTs, re-escalation to the dose level that causes DLT is not permitted. Up to two dose-level reductions per patient are allowed in this study.

Pharmacokinetic studies

To measure the serum concentration of HLX06, blood samples will be collected pre-dose (within one hour), immediately after infusion (within 30 minutes), and at 2, 4, 8, 24, 48, 96, and 168 hours from the 1st and 4th infusion in cycle 1.

Additional time points include pre-dose and after 2nd and 3rd infusions (30 minutes allowable) in cycle 1. Thereafter, the blood levels of HLX06 will be measured before the first infusion of cycle 2 to cycle 6 or up to 24 weeks, whichever comes first; on the 28-day follow-up visit, whenever possible.

Non-compartmental pharmacokinetic analysis will be used to estimate the PK parameters.

Pharmacodynamic studies

Serum concentrations of VEGF-A, soluble VEGFR-1, soluble VEGFR-2 will be measured before and after each infusion in cycle 1 in conjunction with pharmacokinetic studies.

Immunogenicity studies

[1] For patients with hepatocellular carcinoma, mRECIST is used to evaluate treatment effect[6]

Serum samples used to evaluate the presence of antibody against HLX06 will be obtained prior to every infusion of HLX06 in cycle 1 and before the first infusion in subsequent 5 cycles or up to 24 weeks, whichever comes first; at the end of therapy, and at the 28-day follow-up visit, whenever possible.

Table 1. Dose escalation table

No. of patients treated at current dose level	3	6	9	12	15
Escalate if # of DLT	0	1	2	3	3
Remain at the same dose if # of DLT	1	2	3	4	4,5
De-escalate if # of DLT	2	3	4	5	6
Eliminate if # of DLT	3	4	6	7	8

The rules to escalate or de-escalate are as follows:

(a) “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.

(b) When we eliminate a dose, we automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, we stop the trial for safety. In this case, no dose should be selected as the MTD.

(c) If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose.

(d) If the current dose is the lowest dose and the rule indicates dose de-escalation, we will treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point we will terminate the trial for safety.

(e) If the current dose is the highest dose and the rule indicates dose escalation, we will treat the new patients at the highest dose up to maximum 30 patients.

(f). If the number of new patients treated at the current dose reaches 15, stop the trial and determine the MTD based on data from enrolled patients.

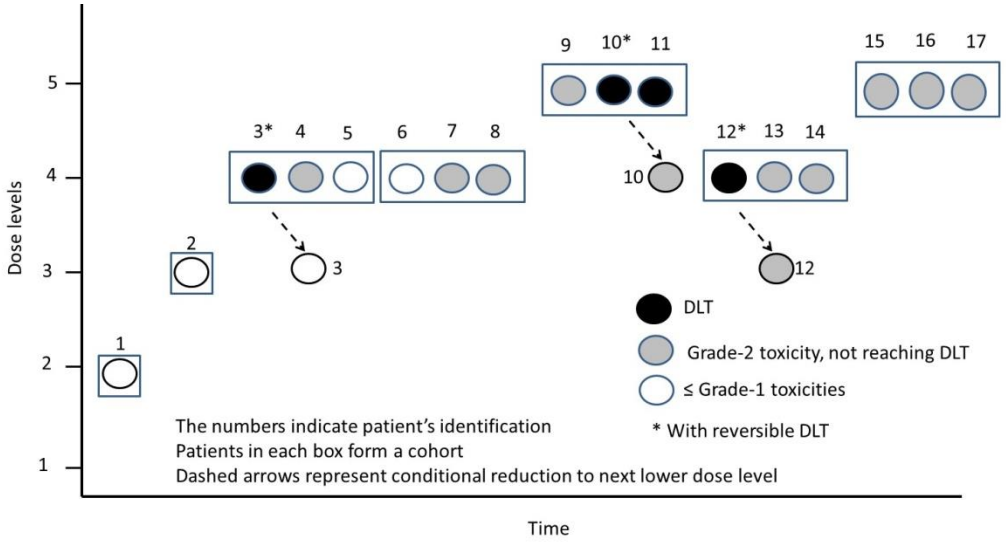

Figure 1. A hypothetical chart of dose escalation and de-escalation.

The number indicates the enrolled patient number. Each circle represents one patient. A square box indicates a cohort. Dotted arrow indicates the lowering to next lower dose if a patient experiences DLT in previous infusions. Open cycle indicates no DLT during the 1st cycle of therapy. Gray cycle indicates grade 2 toxicities during the first cycle. Filled cycle indicates DLT during the first cycle of treatment.

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1. Background Information

Angiogenesis plays an important role in cancer development. More than a dozen different proteins have been identified as angiogenic activators, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor, angigenin. The VEGF family and their receptors (VEGFR) are well characterized for their role in neoplastic angiogenesis. The best known monoclonal antibody targeting angiogenesis is bevacizumab (Avastin®). Bevacizumab has been approved for multiple cancers, including lung, ovarian, colorectal and brain cancer (https://www.avastin.com). Among them, VEGFR2 belongs to type V receptor tyrosine kinase encoded by KDR gene, and is expressed in vascular endothelial cells. It is a primary responder to vascular endothelial growth factor signal that regulates endothelial migration and proliferation. The expression of VEGFR2 can be found in multiple tumor types, including angiosarcoma, Kaposi sarcoma. In epithelial carcinoma, VEGFR2 expression can be found in mesothelioma, non-small cell lung cancer, and embryonal carcinoma[7]. The tissue levels of VEGF-C and VEGFR2 significantly correlate with the progression and prognosis of cancer.[8]

Targeting angiogenesis using either small molecule inhibitors or biological agents have been widely used in current cancer management. Current approved anti-angiogenesis biological agents include bevacizumab, ramucirumab, aflibercept. Among them, ramucirumab (IMC-1121B) targets vascular endothelial growth factor receptor 2 (VEGFR2). Ramucirumab has been approved for use in combination with paclitaxel for second-line treatment of patients with advanced gastric or gastroesophageal junction adenocarcinoma[9].

Ramucirumab is a fully human IgG1 monoclonal antibody that binds with high affinity to the extracellular domain of VEGFR2. It was discovered from an antibody phase display library from pooled B lymphocytes of healthy human donors. The EC50 of ramucirumab is approximately 0.15 nM. A crystal structure analysis demonstrates the binding of its Fab to domain 3 of VEGFR2 near N-terminus. It blocks the VEGF signaling by both steric blocking of its ligand and changing the receptor conformation[9].

1.2. Rationale to develop new anti-VEGFR2 monoclonal antibody

Although ramucirumab has been approved for gastric cancer, its improvement in overall survival is still not satisfactory. It prolongs the overall survival by 6 weeks when combined with paclitaxel. So far, there is not biomarker available to predict the efficacy of ramucirumab.

Therefore, a new monoclonal antibody also targeting VEGFR2 might provide better efficacy for cancer patients.

HLX06 is a new monoclonal antibody targeting VEGFR2. It has better binding affinity to VEGFR2, and also binds to different region in VEGFR2. *In vitro* studies have demonstrated the growth inhibition of human endothelial cells, and HLX06 has shown growth inhibition of tumors in xenogeneic studies.

Nonclinical studies up to weekly 150 mg/kg in *cynomolgus* monkeys for 13 weeks have shown good tolerability without evident toxicities (please refer to Investigator's brochure). HLX06 shows cross-reactivity to both monkey and human VEGFR2, but does not bind rodent VEGFR2.

This study is the first-in-human study to address the safety and tolerability of HLX06 in patients with metastatic or recurrent cancer.

1.3. Potential Risk and Benefits

1.3.1. Known potential risks

HLX06 has not been tested in human before and its potential toxicities are unknown. Based on the nonclinical studies, HLX06 reacts with human and monkey VEGFR2, but not murine VEGFR2, so its prediction of toxicities in human is based on the monkey study with limited numbers. However, HLX06 is not the first monoclonal antibody targeting VEGFR2 to go into humans. Ramucirumab, a VEGFR-2 monoclonal antibody, has been widely used in different cancers with more than 1000 patients. When ramucirumab is used alone in a patient population similar to this study, the most common toxicity is grade-3 hypertension.[10] No increased risk of bleeding, venous thrombosis, proteinuria, or gastrointestinal perforation occurred[9]. However, when ramucirumab is used in combination with cytotoxic agents, it has a different toxicity profile. In the study with paclitaxel, the most common grade-3 or higher toxicities are neutropenia, leucopenia, hypertension, fatigue and abdominal pain.[11] When ramucirumab is used with FOLFOX chemotherapy as first-line therapy for colorectal cancer patients, the most common grade-3 or higher toxicities are neutropenia, fatigue, and neuropathy[12]. Based on the same target and similar mode of action by HLX06 in cancer cells, we expect the toxicity profile is likely to be similar to those observed in ramucirumab monotherapy. Although ramucirumab appears to be more tolerable than bevacizumab, Investigators have to remain vigilant given that no prior safety data are available for HLX06.

1.3.2. Known potential benefits

This study enrolls metastatic or recurrent patients who have failed standard therapy. Its benefit for patients who participate in this study remains unclear. However, based on prior study of ramucirumab in gastric cancer patients who have failed first-line chemotherapy, ramucirumab monotherapy improves overall survival up to two months[13]. When ramucirumab was tested at different doses in metastatic patients with different cancer types, 60% had stable disease with median duration of 12.7 months[10, 14]. Stable disease ≥4 months occurred in 20% of patients without warning toxicities. Based on similar mode of action, we expect the activity of HLX06 likely to be similar to that of ramucirumab.

2. OBJECTIVES

2.1. Primary Objective

To identify safety and the maximum tolerated dose (MTD) of HLX06 in patients with advanced or metastatic tumors refractory to standard therapy.

2.2. Secondary Objectives

- The pharmacokinetics of HLX06 at different doses in patients.
- The pharmacodynamics of HLX06 at different doses in patients.
- The immunogenicity of HLX06 in human beings.
- The anti-tumor effects of HLX06 in patients.
- The potential prognostic and predictive biomarkers of HLX06 for advanced solid tumors.

3. OVERVIEW OF STUDY DESIGN AND ENDPOINTS

3.1. Description of the Study Design

This study is a prospective, open-label, dose-escalation study of HLX06 in patients with metastatic or recurrent solid tumors who have failed standard therapy.

This study integrates the modified accelerated titration design 2A (ATD) and Bayesian optimal interval design (BOIN) to determine the MTD of HLX06[1, 2]. The safety and PK profiles, and immunogenicity as well as the preliminary efficacy will also be examined.

Eligible patients who fulfill the eligibility criteria will receive weekly infusion of HLX06 at the assigned dose level until disease progression or to the maximum of one year, withdrawal from study or death, whichever comes first.

Each cycle of treatment is comprised of 4 doses of investigational product administered weekly.

This study plans to enroll a maximum of **30** patients. *Patients who withdraw from the study for reasons not related to treatment-emergent toxicities during the first cycle will be replaced.*

3.1.1. Accelerated titration design and cohort size

In the ATD 2A design, the study starts with acceleration phase. In this phase, each cohort consists of one NEW patient for each dose level. After first cycle of treatment, the patient will be evaluated for the toxicities in last cycle. If this patient does not have DLTs, the next patient is allowed to receive the treatment at the next higher dose level.

In the acceleration phase, the newly enrolled patients start at the highest dose level, in which no moderate toxicities are observed in prior patients.

When the first instance of first-cycle DLT or the second instance of first-cycle grade≥2 toxicities of any types occurs, acceleration phase ends and the cohorts for the current dose level expand to three NEW patients and the study switches the BOIN design phase.

In the acceleration phase, intra-patient dose escalation is NOT allowed.

3.1.2. Bayesian optimal interval design and rules of dose escalation and de-escalation

After the acceleration phase, the study uses BOIN design to determine rule of dose escalation and de-escalation. First, the target toxicity rate in this study is set at **30%,** which is the most

common toxicity rate for conventional 3+3 design, indicating that for an oncologic agent, the toxicity rate higher than 30% is NOT desirable[15].

Different from the rule-based 3+3 design, the decision to escalate or de-escalate in BOIN design is based on the posterior probability of DLTs from updated information. The probability of DLTs is determined by the number of DLTs and the cumulative number of patients treated at the current dose. The safety boundary to escalate the dose is set at 70% of target toxicity rate (i.e. 21%); and the toxicity boundary is, at 130% of target toxicity rate (i.e. 39%), respectively. If the probability of DLTs at the current dose level falls below 21%, the dose in the next cohort escalates to the next higher level. By contrast, when the probability of DLT at the current dose level arises above 39% (130% of target rate), the dose in the next cohort de-escalate to the next lower level. The dose level for the next cohort remains the same if the probability of toxicity is within the safety and toxicity boundary. The enrollment continues until the maximum of 30 patients are reached.

The detailed rule of dose escalation and de-escalation is tabulated in Table 1.

There are also two pre-set EARLY STOPPING RULES in this study.

- Stop the trial if the lowest dose (dose level 1) is eliminated due to overt toxicities.
- Stop the trial and estimate the MTD if the number of new patients treated at the current dose level reaches 15

The detailed statistical methods for dose escalation and de-escalation and estimation of MTD are described in Section 11. This study uses R software and BOIN package for setting up the specifications. The detailed R codes for this study are described in the Appendix (Section 15.5).

Patients who experience DLTs may be allowed to continue the treatment at the next lower dose level after the toxicities revert to grade≤1 in 28 days after last infusion, if the Investigator judges that the patient still meet the inclusion criteria and might benefit from continuous treatment.

For patients who experience DLTs, re-escalation to the dose level causing DLT is not permitted. Up to two dose-level reductions per patient are allowed in this study.

3.2. Justification of dose levels and starting dose

Six dose levels are planned: 250, 500, 750, 900, 1200, 1500 mg flat dose. The reason for using flat dosing instead of body weight-adjusted dosing is based on previous population pharmacokinetic studies for multiple monoclonal antibody drugs[3, 16, 17]. Patients will be assigned to a dose level in the order of study entry. The starting dose of 500 mg (dose level 2)

is based on ICH guidance and determined to be equal to 1/6 of the human equivalent dose of the highest non-severely toxic dose (HNSTD)[4, 18].

In BOIN design, the decision to escalate or de-escalate is based on the probability of toxicities from updated information on pre-defined toxicity rate, which is set at 30% in this study. When the probability of DLT is lower than 21% (70% of target rate), the dose in the next cohort escalates to the next level. By contrast, when the probability of DLT is higher than 39% (130% of target rate), the dose in the next cohort de-escalate to the next lower level. The enrollment continues until the maximum of 30 patients is reached.

The rule of dose escalation and de-escalation is tabulated in Table 1.

There are two early stopping rules set in this study.

- Stop the trial if the lowest dose (dose level 1, i.e. 250 mg) is eliminated due to overt toxicities.
- Stop the trial and estimate the MTD if the number of new patients treated at the current dose level reaches 15

The detailed statistical methods for dose escalation and de-escalation and determination of MTD are described in Section 11. Description of Statistical Methods. The detailed R script for this study is described in. Section 15.5.

3.3. Treatment duration

If the patients experience no adverse reactions that lead to treatment delay or discontinuation, treatment continues weekly until disease progression, to the maximum of one year, withdrawal from study or death, whichever comes first.

Detailed procedures for the evaluation and treatment are described in Section. 7.2.

Toxicities will be evaluated and graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE) 4.0 or until the toxicities revert to grade ≤1.

Serial serum samples will be collected during the 1st and 4th week of 1st cycle of treatment at scheduled time points for determination of the PK of HLX06. Additional time points include before and after 2nd and 3rd infusions in cycle 1. Thereafter, the blood levels of HLX06 will be measured before and after the first infusion in each cycle up to 24 weeks, , and on the 28-day follow-up visit (Follow-up Visit 1) whenever possible.

This study also incorporates optional pharmacodynamic study by examining the serum levels of VEGF-A, soluble VEGFR-1, soluble VEGFR-2 before and after first and 4th infusion in cycle 1 in conjunction with pharmacokinetic studies.

3.4. Follow-up period

The details of follow-up are described in Section 7.3.

3.5. Primary endpoints of the study

- Primary outcome measures
- Numbers and percentage of patients with adverse events (AEs).
- Maximum tolerated dose of HLX06.

3.6. Secondary endpoints of the study

- Maximum concentration (C_{max}) in different cohorts.
- Minimum concentration (C_{min}) in different cohorts.
- Area under concentration ($AUC_{0\text{-}tau}$) in different cohorts.
- Half-life ($T_{1/2}$) of HLX06 in different cohorts.
- Clearance (CL) rate of HLX06 in different cohorts.
- Volume of distribution (V_{ss}) at steady state in different cohorts.
- The presence and percentage of anti-HLX06 antibody (immunogenicity).
- Disease control rate
- Overall response rate.
- Duration of response

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study population

A maximum of 30 patients will be enrolled (if no patients require replacement). Patients with metastatic or recurrent solid tumors who have failed standard therapy can be considered eligible for enrollment.

4.2. Inclusion criteria

- Eligible patients must be 18-years of age or older or per local regulations.
- Patients with histologically-proven measurable or evaluable advanced or metastatic solid tumors who have failed standard therapy or for whom no standard therapy is available. (For patients with hepatocellular carcinoma, the diagnosis needs to be supported by dynamic CT/MRI, if pathological confirmation is not attainable)
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 at the time of study entry.
- Able to provide informed consent.
- A life expectancy longer than three months.
- Adequate hematologic functions, as defined by: absolute neutrophil counts ≥ 1500/mm^3; a hemoglobin level ≥ 10 gm/dL; a platelet count ≥ 100,000/mm^3.
- Adequate hepatic function defined by: a total bilirubin level ≤ 1.5x of upper limit of normal (ULN); aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤ 2.5 x of ULN or ≤ 5x of ULN in known hepatic metastases or with primary hepatocellular carcinoma.
- Adequate renal function, as defined by the creatinine clearance rate ≥ 50 mL/minute by Cockcroft-Gault formula.
- Adequate cardiac function defined as left ventricular ejection fraction (LVEF)≥ 50%.
- Use of effective contraceptive measures if procreative potential exists.
- At least 28 days from prior major surgery, prior cytotoxic chemotherapy, or prior therapy with investigational agents (or medical device) or local radiotherapy before 1st infusion of HLX06.
- For patients with hepatocellular carcinoma, their Child-Pugh score has to be A.
- Able to be followed up as required by the study protocol.
-

The ECOG performance table is listed in Appendix 15. Detailed the Child-Pugh score is listed in Appendix 15.2.

4.3. Exclusion criteria

- Patients with large centrally located pulmonary lesions adjacent to or invading large blood vessels.
- Hemoptysis more than ½ teaspoon (approximately 2-3 mL) of red blood per day.
- Patients who still have ≥ grade 2 toxicities from prior therapies.
- Concurrent unstable or uncontrolled medical conditions with either of the followings:
    - Active systemic infections;
    - Poorly controlled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥100 mmHg), or poor compliance with anti-hypertensive agents;
    - Clinically significant arrhythmia, unstable angina pectoris, congestive heart failure (class III or IV of New York Heart Association [NYHA]) or acute myocardial infarction within 6 months;
    - Uncontrolled diabetes or poor compliance with hypoglycemics;
    - The presence of chronically unhealed wound or ulcers
    - Other chronic diseases, which, in the opinion of the investigator, could compromise safety of the patient or the integrity of study.
- Newly-diagnosed or symptomatic brain metastases (patients with a history of brain metastases must have received definitive surgery or radiotherapy, be clinically stable, and not taking steroids for brain edema). Anticonvulsants are allowed.
- Any concurrent malignancy other than basal cell carcinoma or carcinoma in situ of the cervix. (Patients with a previous malignancy but without evidence of disease for ≥ 3 years are allowed to participate).
- Pregnancy (confirmed by serum beta human chorionic gonadotropin [ßHCG]) or breast-feeding (for female patients only).
- A known history or clinical evidence of a deep vein or arterial thrombosis, or pulmonary embolism within 6 months of first infusion of HLX06.
- Less than six weeks from last infusion of ramucirumab, or any other anti-VEGF monoclonal antibody therapy (Last treatment with other monoclonal antibodies targeting proteins other than anti-angiogenic factors is permitted if ≥ 4 weeks prior to the first infusion of HLX06).

- Proteinuria ≥ 2+ in routine urinalysis (patients with a protein value of ≤500 mg confirmed by a 24-hour urine collection are eligible).
- Known history of human immunodeficiency virus infection (HIV).
- The patient is the investigator, sub-investigator or any one directly involved in the conduct of the study.

4.4. Randomization and blinding

- Blinding is not applicable as this is an open-label study.
- The patients of the study are not randomized.

The study site will contact the Sponsor or its designee for treatment assignment once a patient is determined to be eligible for enrollment. Patients who meet all the eligibility criteria will be assigned a number and the dose level for the first infusion as determined by the Sponsor or its designee. Once assigned, numbers for any screening failures, non-treated, non-evaluable, or discontinued subjects will not be re-used.

5. STUDY DRUG AND ITS PREPARATION

All protocol-specified investigational and non-investigational products are considered study drugs.

5.1. Investigational product (IP) and non-investigational product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A test article or pharmaceutical form of an active ingredient or placebo that is tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, used for an unapproved indication, or used to gain further information about an approved use.

The IP is HLX06 in this study.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

5.2. Description of IP

HLX06 is recombinant human IgG1 monoclonal antibody directed against human VEGFR2. The study agent will be provided by the Sponsor. The rest of medications are provided by study sites.

5.3. Product appearance, storage, stability and formulation

HLX06 is supplied in a single-use 10 mL vial. Each vial contains 100 mg active drug in 10 mL clear, colorless solution and should be stored at 2-8 ºC. The drug is expected to be stable up to two years when stored at 2-8 ºC. In addition to the active ingredient, the main ingredients in the solution are sucrose, sodium chloride, sodium citrate, and polysorbate 80. Detailed information on formulation is described in the Investigator's brochure. The product storage manager should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns

regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact the Sponsor immediately.

Investigational product should be stored in a secure area per local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study patients. Investigational product must be dispensed only from official study site by authorized personnel according to local regulations.

5.4. Packaging and labeling

The investigational product will be packaged and labeled per current good manufacturing practices (GMP).

5.5. Ordering investigational products

Clinical supplies may be requested by completing a Request Form and faxing it or e-mail it to the Drug Supply Coordinator of the Sponsor or its designee.

5.6. Preparation of investigational product and administration

HLX06 is intended for **intravenous** injection only with final concentration no more than 10 mg/mL

To minimize the error in the adjustment of infusion rate, HLX06 is constituted to the final volume of **200 mL** with normal saline and infused intravenously in **two hours**, regardless of the assigned dose level. Diluted HLX06, if not used in 4 hours, should be stored at 2-8 ºC and be used in 24 hours.

The following procedure is required to prepare the HLX06 solution.

Confirm the dose needed to be infused and calculate the volume needed. Draw up the volume of a vial of HLX06 using a sterile syringe.
Fill HLX06 in a sterile evacuated container or bag such as glass containers, polyolefin bags (ethylene vinyl acetate bags, DEHP plasticized PVC bags, or PVC bags).
Repeat the procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
Dilute the drawn HLX06 with sterile 0.9% saline solution to make the final volume of 200 mL.

Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical). Affix the infusion line and prime it with diluted HLX06 before starting the infusion. **Set the infusion rate to 100 mL per hour**.
At the end of infusion period, flush the line with sufficient amount of normal saline.

5.6.1. Three DON'Ts in preparation of HLX06 for infusion

- DON'T enter the vial more than once.
- DON'T piggyback to the patient's other infusion line. HLX06 should be infused using a separate infusion line.
- DON'T administer HLX06 as an intravenous push or bolus injection.

5.7. Drug accountability

HLX06 must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the investigational product in a Drug Accountability Log, a copy of which must be given to the Sponsor at the end of the study. The Drug Accountability Log will record the investigational products received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

5.8. Disposal of investigational product

If investigational products are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. Unused HLX06 should be returned to the Sponsor after the study. Used vials can be disposed at the study site following institutional guidelines for investigational product. Vials without proper labeling or suspected of contamination should not be used and returned to the Sponsor.

6. ASSESSMENT OF SAFETY AND MANAGEMENT OF TOXICITIES

6.1. Dose limiting toxicities (DLTs)

DLTs are side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment in a clinical study. We use Common Toxicity Criteria for Adverse Events (CTCAE) 4.0 for grading of toxicities in this study.

The definition of DLTs in this study is the toxicities during the first cycle of treatment:

A DLT will be considered to be IP-related unless there is a clear, well-documented, alternative explanation for the toxicity. Delayed DLTs are adverse events that meet the criteria of DLTs that occur after the first cycle of treatment. Delayed DLTs need to be evaluated on a case-by-case basis to make sure that there is no cumulative damage to vital organ function.

Delayed DLTs will also be considered to estimate the MTD for HLX06 in this study.

All adverse events that meet DLT or delayed DLT criteria, as well as any Grade 3 or 4 infusion reactions no matter whether the event is a DLT must be reported to the Sponsor or its designee, within 24 hours.

6.2. Stopping rules for clinical deterioration

Clinical deterioration is defined by the clinical condition of the patient has worsened and, in the Investigator's opinion, is attributable to disease progression. Such deterioration is not likely to be reversed with additional administration of Investigational Product and supportive care. The decision to continue or stop treatment should be discussed with the Medical Monitor and documented in the study records.

Events that suggest clinical deterioration include, but not limited to the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following
  - Pathologic bone fracture in the region of cancer involvement
  - Cancer related surgery to bone
  - Spinal cord or nerve root compression
- Bladder outlet or urethral obstruction
- Development of new central nervous system metastases

- Patients that develop new CNS metastases in the setting of improving baseline disease may have focal radiation, resection, or other local curative procedures performed after consultation with the Medical Monitor.
- If continued study therapy is deemed to offer the patient potential benefit, patients may be allowed to restart study therapy after recovery from symptoms related to the procedure performed (i.e., local edema) and steroid dosing at < 10 mg prednisone/day or equivalent.
- Patients that have locally curative procedures while on study drug and subsequently develop new CNS metastases at a subsequent imaging assessment should discontinue study therapy and enter the follow-up period.
- Or any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the patient even in the absence of any such documented clinical events.

6.3. Strategies to mitigate the risk of severe adverse events and toxicities

To mitigate the risk of HLX06 first-in-human use, the interval of first infusion of investigational product between NEW patients in a cohort is **24 hours or longer.**

6.4. Management of possible toxicities

HLX06 has not been used in human beings before. There is no clinical experience to define expected toxicities to humans. Based on its mode of action, the spectrum of toxicities is expected to be similar to what have been described for anti-angiogenesis agents, such as bevacizumab, ramucirumab or other small molecule inhibitors for anti-angiogenesis (e.g. sunitinib, sorafenib). The following are the common or severe toxicities by bevacizumab and ramucirumab and their respective management.

Allergic reaction/hypersensitivity and infusion-related reactions: Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related adverse events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated. The common agents used to treat hypersensitivity agents are anti-histamine, H2-blockers, corticosteroid. Severe anaphylactic reactions might require epinephrine treatment. Infusion reaction should be graded according to NCI CTCAE criteria. Treatment recommendations are as follows:

- **Grade 1 symptoms:** If the Investigator assesses that it is a mild reaction and infusion interruption is not indicated, the prophylactic pre-medications are recommended: diphendydramine 30-50 mg (depending on institutional availability or equivalent medications), acetaminophen 325-500 mg PO at least 30 minutes before additional IP infusion.
- **Grade 2 symptoms:** If the Investigator assesses that it is a moderate reaction, requiring therapy or infusion interruption, stop the IP infusion and begin with intravenous infusion of normal saline, and treat the patients with diphenhydramine 30-50 mg (or equivalent medications) intravenously, and dexamethasone 10 mg (or corticosteroids with equivalent potency) intravenously. After the symptoms have subsided, restart the infusion at 50% of original infusion rate. Monitor the patient closely. If the symptoms recur, no further IP infusion at that visit. Prophylactic pre-medications with diphenhydramine, acetaminophen and corticosteroid are indicated for future infusion of IP.
- **Grade ≥3 symptoms:** It is severe reaction, and recurs, or does not rapidly respond to symptomatic treatment and interruption of infusion, stop the infusion of IP immediately. Consider 0.2 to 1 mg of 1:10,000 solution of epinephrine for subcutaneous administration. Diphenhydramine 30-50 mg intravenous with methylpredisolone 100 mg (or equivalent) intravenously, as needed. Hospitalization might be needed for possible clinical sequelae.

Hypertension: Hypertension is among the most common toxicities of anti-angiogenic therapy. The incidence of hypertension could reach 20% by a single anti-angiogenic agent. Initiation of antihypertensive medications should be considered when BP is >140/90mmHg or if there is an increase in DBP ≥20mmHg. If SBP >160mmHg, DBP >100mmHg, hypertensive crisis or if antihypertensive interventions do not provide appropriate BP control, the dose level of HLX06 should be decreased or held until antihypertensive therapy is effectively titrated. Although appropriate BP control is essential, excessive lowering of BP may also have detrimental cardiovascular consequences; careful selection of doses and close BP monitoring are crucial to avoid episodes of hypotension. Multiple antihypertensive drugs are being used to treat anti-angiogenic therapy-induced hypertension including calcium channel blockers, inhibitors of the renin-angiotensin system, beta-blockers and diuretics. At this time, however, no clinical evidence favoring one antihypertensive agent over another is available [19].

Bowel perforation: Clinical trials have revealed that 1-4% of colorectal cancer patients receiving bevacizumab could develop spontaneous bowel perforation. It could also occur in patients who have no involvement of cancer in the gastrointestinal tract. Several risk factors for bevacizumab-associated bowel perforation have been identified, including a history of peptic ulcer disease, diverticulitis, colitis, intestinal obstruction, tumor necrosis, recent sigmoidoscopy or cumulative dose of bevacizumab, radiotherapy, or emergent surgery while receiving bevacizumab, it is still unclear which patients are specifically at risk for this complication. Gastrointestinal perforation could lead to peritonitis, requiring emergent operative intervention, fistula formation or intra-abdominal abscess[20]. Bowel perforation could be hard to diagnose in patients without symptoms. If the symptoms are present, it usually presents as acute abdomen due to peritoneal contamination, hemoperitoneum, or free intra-abdominal air, or intra-abdominal abscess. The management of bowel perforation depends on the timing of the presentation, the overall condition of the patients and the goals of treatment. Medical treatment is usually ineffective. More likely, patients need to receive surgical intervention. The long half-life of monoclonal antibody increases the risk of unplanned, urgent surgical procedures. For patients who have received HLX06 therapy, surgery within 28 days following their last treatment should be avoided. If surgery is necessary, risk-and-benefit assessment should be conducted by experienced surgeons.

Severe proteinuria: This is another common side effects observed in anti-angiogenic therapy. Severe proteinuria including nephritic syndrome may cause significant morbidity with a possible consequence of renal failure and fatality. It is recommended to suspend anti-angiogenic therapy at least temporarily for proteinuria ≥2 g/24 hours and to discontinue the therapy for nephrotic syndrome. The risks of severe proteinuria include higher dose of therapy, concurrent use of chemotherapy and renal cell carcinoma.[21] There are no evidence-based guidances for the management of anti-antigenic therapy-induced proteinuria. If proteinuria is ≥ 2 g/24 hours during HLX06 therapy, stop the therapy, and the patients might resume the therapy after proteinuria decreases to <2 g/ 24 hours at the next lower dose level, if the benefit of HLX06 is deemed to outweigh the risks, as judged by the Investigator.

Bleeding: This is a frequent complication of anti-angiogenic therapy. Two meta-analyses have found that the use of bevacizumab in combination with chemotherapy for the treatment of various tumor types conferred an increased risk of severe and fatal bleeding events and treatment-related mortality versus chemotherapy alone. Most cases involve low-grade mucocutaneous bleeding that can be managed by local treatment and usually does not interrupt

treatment. Epistaxis is another common bleeding. Studies have shown that the rates of grade 1-2 epistaxis range from 5-26%. Mild-to-moderate Epistaxis is usually managed conservatively. However, in severe cases, operative hemostatic intervention might be indicated. In such cases, otolaryngologists with experience in managing drug-induced bleeding should be consulted. Intracranial hemorrhages are associated with bevacizumab use especially in patients with glioblastoma multiforme[22]. The highest incidence of high-grade bleeding is associated with non-small cell lung cancer, especially with squamous cell histology. This risk is particularly high in patients with persistent hemoptysis before study. This led the exclusion of patients with this histology and patients with hemoptysis in most of subsequent clinical studies for lung cancer. Well patient selection might be the best strategy to prevent this complication. Once bleeding is identified, appropriate management is based on the site and the degree of bleeding. In sites where bleeding cannot be controlled by compression, or when the degree of bleeding is severe, surgical intervention might be needed for better control.

Poor wound healing and fistula formation: Anti-angiogenic therapy compromises neovasculization, and affects wound healing. Pooled analysis from bevacizumab studies found 13% wound-healing complication. When surgery was done within 2 weeks after last bevacizumab dose, the risk of poor healing is higher. So far, specific recommendation for the management of poor wound healing has not been established. General recommendation is that surgery should be avoided within 60 days of bevacizumab when chemotherapy is used together or within 28 days when monotherapy is used.[23]

Thromboembolism: Anti-angiogenic therapy not only increases the risk of bleeding, it also increases the risk of thromboembolism[22]. The risk factors associated with thromboembolism is age older than 65, advanced cancer, and the location of tumors. The incidence of thromboembolism was highest in patients with colorectal cancer. However, there is not standard recommendation for prevention of thromboembolism by prophylactic use of anti-coagulants. The Investigator should remain high alert on the emergence of thromboembolism and manage the complication accordingly.

Tumor lysis syndrome: Tumor lysis syndrome has been described in patients receiving chemotherapy/ bevacizumab or sunitinib[24]. This may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic

acidosis (acute renal failure and lactic acidosis). The management of tumor lysis syndrome induced by anti-angiogenic therapy is similar to that by other anti-cancer agents. In general, resumption of anti-cancer therapy is judged by the patient's condition and the decision of Investigator.

7. STUDY SCHEDULES AND PROCEDRUES

The study of each patient is divided into three periods: screening, treatment and follow-up.

7.1. Screening period

As soon as a patient is considered for this study, and before performing any study procedures, the patient needs to have the nature of the study explained and will be asked to provide a written informed consent. A written, signed and dated, informed consent form (ICF) must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the patient and a copy will be filed in the medical record. The original version needs to be kept on file with the study records.

Screening assessments must be completed within 28 days prior to the first infusion of the IP (HLX06). Any results falling outside of the reference ranges may be repeated at the discretion of the investigators.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients, and to ensure that the study results can be used. It is imperative that patients fully meet all the eligibility criteria. The study population and detailed Inclusion and Exclusion criteria are listed in Section 4 .

Baseline imaging performed as part of the patient's previous routine care before signing the ICF and completed within 42 days before the first infusion of IP can be used as pre-treatment imaging, without the need to repeat the imaging studies.

If there is a question about eligibility and enrollment, the Investigator should consult with the Sponsor's Medical Monitor, or designee, before enrolling into the study.

The screening procedures can be done at inpatient or outpatient setting based on the situation in different site.

7.1.1. Assessments in the Screening Period

Patients will be evaluated for entry criteria during the Screening Period within 28 days before the first infusion of study drug. The following procedures and evaluations need to be completed for each patient before Day 1:

1. A written, signed-and-dated informed consent should be obtained before any screening procedures and receiving study drugs.

2. Inclusion and exclusion criteria are cross-checked.
3. Demographics and medical history (to include collection of prior medications administered to the patient during the Screening Period, prior and concurrent medical conditions, and baseline signs and symptoms)[2]
4. Diagnosis confirmation and stage[3]
5. History of tumor-specific therapy including chemotherapy and radiotherapy or any other forms of therapy.
6. ECOG performance status
7. Vital signs (temperature, pulse, respiratory rate and blood pressure), weight and height.
8. Physical examination including an elective neurological examination.
9. Documentation of disease assessment
10. Baseline condition assessment (record the amount of hemoptysis, if present).
11. Documentation of measurable diseases.
12. Review of pathology reports including mutation status
13. Complete blood count (CBC) with differentials and D-dimer.
14. Coagulation profile: prothrombin time, partial thromboplastin time, international normalized ratio (PT/INR/PTT).
15. Blood chemistry profile: Fasting glucose, blood urea nitrogen (BUN), creatinine, ALT, AST, total protein, albumin, globulin, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, lactate dehydrogenase (LDH), IgG and IgM.
16. Lipid profile: total cholesterol, triglyceride.
17. Thyroid function tests: thyroid-stimulating hormone (TSH), T3, free thyroxine (FT4)
18. Serum lipase and amylase.
19. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), Hepatitis C antibody (anti-HCV).
20. Tumor markers (CEA, CA199, CA125, CA153, alpha-fetoprotein and PSA[5])
21. Serum βHCG test for female patients with child-bearing potential[6].

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[2] Baseline signs and symptoms: Clinical adverse events occurring after signing informed consent, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF
[3] If all patients should have confirmed pathologic diagnosis, if not, a pathology review might be necessary.
[4] If no prior record of pathologic diagnosis is available, a tumor biopsy is required.
[5] PSA is needed for patients with prostate cancer.
[6] Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child-bearing potential.

22. Urinalysis[7].
23. Chest radiograph (X-ray)
24. 12-lead electrocardiogram (ECG).
25. Tumor imaging with contrasted computerized tomography or MRI (chest, abdomen and pelvis) for tumor assessment (if the imaging studies are less than 6 weeks before 1st infusion of IP, no need to repeat the studies).
26. Contrasted brain CT/MRI (if the imaging studies are less than 8 weeks before 1st infusion of HLX06, no need to repeat the test).
27. Cardiac ultrasound or a MUGA scan
28. Bone scan (if signs or symptoms suggestive of bone metastases are present). Confirmative X-ray, CT or MRI for bone metastases for patients with positive bone scan. *The selection of imaging modality is based on the discretion of investigators for the benefit of patients.*
29. Concomitant medications including alternative medicines.
30. Assessment of adverse events from prior therapies.

7.2. Treatment period

The treatment of the study is divided in cycles with associated evaluation and procedures that must be performed at specific time points. Subjects who meet inclusion/exclusion criteria may start the Investigation Product (IP) treatment within 28 days of Screening period. Each cycle of treatment is FOUR weeks. Enrolled patients will receive FOUR weekly infusions of IP in a cycle.

Following cycle 1, the decision whether to treat the patients with additional cycles of IP and which dose level to use in the next cycle will be determined by the toxicities of the prior cycle (refer to Section 7.2.2.1).

A patient who is withdrawn from the study before the completion of the first cycle for a reason other than treatment-emergent toxicities will be replaced.

[7] Urinalysis includes: color, turbidity, specific gravity, pH, leukocyte, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, blood cells. If the urinalysis indicates significant proteinuria (> 30 mg or >=2+ by urine dipstick), urinalysis must be repeated. If the repeat dipstick protein value is >30 mg or >= 2+ by urine dipstick, 24-hour urine collection is required to calculate total protein.

7.2.1. Interval of the first infusion between new patients in a cohort

The interval of the first infusion between NEW patients in a cohort is **24** hours or longer, regardless of the dose level. This is to ensure the safety of patients in a cohort, in case there were excessive toxicities.

7.2.2. The requirement of hospitalization for the infusion of IP

The Investigator may hospitalize the patients for the first infusion of IP and the PK/PD studies in cycle 1. Based on the reactions during and after the first infusion in cycle 1, it is up to the Investigator to determine whether extended hospitalization for observation and PK/PD studies are necessary. It is also the Investigator's discretion to determine whether hospitalization is needed for subsequent infusions.

7.2.2.1. Determination of the dose level for the first infusion in a cycle

This study adopts an adaptive trial design, which is different from conventional 3+3 design. Please refer to Section 3 for the detail of study design.

In the accelerated phase, Investigators and the study staff need to assess the toxicities in the first cycle and communicate with the Study Monitor or its designee the dose level before the first infusion in the next NEW patient.

7.2.2.2. Pre-medications for the first and subsequent infusions in a cycle

Primary prophylaxis for first infusion reaction of HLX06 is **NOT** mandatory. If the patients experience infusion reactions, allergic reactions, nausea, vomiting or other symptoms/signs related to infusion of experimental drugs, pre-medications to mitigate these reactions with antihistamine, acetaminophen, corticosteroid or 5-HT3 antagonist are permitted in subsequent infusions. Investigators could also follow institutional guidelines for pre-medications for infusion-related conditions.

7.2.2.3. Procedures for the first infusion in a cycle.

For preparation of IP and the requirement for infusion set, please refer to Section 5.6.

Treatment will begin with the first intravenous infusion of IP (Day 1) and will continue every 7 days for a total of 4 doses (Days 1, 8, 15 and 22) in a cycle with the response assessment described in Section 8.

The followings are the procedure required before the first infusion in each cycle: *(the laboratory tests before the first infusion may be waived, if the interval between screening tests and first infusion is less than 7 days, and the Investigator judges that the patient's condition remains stationary)*.

1. Vital sign measurements to include temperature, pulse, and blood pressure will be obtained as defined in the Section 14.
2. Weight
3. Physical examination (including measurement of vital signs as well as pulmonary, heart, abdomen, and skin assessments with selective neurological examination)
4. ECOG performance status
5. 12-lead ECG[8]
6. Complete blood count (CBC) with differentials, and D-dimer
7. Tumor markers[9] (CEA, CA199, CA125, CA153, alpha-fetoprotein and PSA[10])
8. Coagulation profile: prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR).
9. Blood chemistry profile: Fasting glucose, blood urea nitrogen (BUN), creatinine, ALT, AST, total protein, albumin, globulin, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, lactate dehydrogenase (LDH), IgG, and IgM **[11]**
10. Thyroid function tests: thyroid-stimulating hormone (TSH), T3, free thyroxine (FT4)[12]
11. Urinalysis.
12. Urine pregnancy test for female patients with child-bearing potential.[13].
13. Infusions of IP (after all other evaluations for the visit according to the Time and Events Table have been completed except for the post-infusion pharmacokinetic samples)

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[8] ECG must be done predose and within 30 minutes after the end of 1st infusion.
[9] If the tests have been done during the Screening period, no need to repeat the tests before 1st infusion in cycle 1. These should be done every 8 weeks in the first 24 weeks and every 12 weeks thereafter.
[10]For prostate cancer only.
[11] Lab data must be performed and reviewed before dosing. Any new Grade ≥ 3 laboratory abnormality, such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk before dosing. In the event of uncertainty, the Medical Monitor should be contacted.
[12] If thyroid function tests have been performed in the Screening period, no need to repeat before the first infusion in cycle 1, but repeat the thyroid function tests every 8 weeks before the first 24 weeks and every 12 weeks after 24 weeks.
[13] In the screening period, serum pregnancy test is used. Before the first infusion, urine pregnancy is used. A positive urine pregnancy test must be verified by a serum βHCG test. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child-bearing potential.

14. Assessment of adverse events
15. Obtaining serum samples for pharmacokinetics as outlined in Section 9 (post-infusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)[14]
16. Obtaining serum samples for pharmacodynamics [15]
17. Obtaining serum samples for immunogenicity (collected before infusions)

Following Cycle 1, patients may receive additional cycles of therapy until disease progression, up to a maximum of one year, withdrawal from study or death, whichever occurs first. If the patient's disease remains stable and the patient is deemed to benefit from continuous treatment of IP, additional treatment beyond one year will be evaluated on a case-by-case basis and arranged between the Investigator and the Sponsor.

The evaluations performed for the first infusion in subsequent cycles are the same (except for the PK/PD studies) and the results will be recorded on the CRF. Details are tabulated in Section 14.

7.2.2.4. Management for the infusion-related reactions

For patients who experience first infusion reactions, please refer to Section 6.4 for the procedure and management.

7.2.3. Procedures for subsequent infusions in a cycle

Following the first infusion in a cycle, patients may receive additional infusions on day 8, 15 and 22 to complete the cycle of treatment. The maximum duration of IP to be administered to an individual patient in this study is one year.

The evaluations performed for the second to fourth infusion in a cycle are as follows:

1. Vital sign measurements to include temperature, pulse, and blood pressure will be obtained as defined in the Section 14.
2. Weight
3. Elective physical examination (including measurement of vital signs as well as pulmonary, heart, abdomen, and skin assessments)

[14] Detailed pharmacokinetic studies are conducted in the first week in Cycle 1 only.
[15] The samples are collected before and after one hour of first infusion in Cycle 1. Please refer to Section 9 for detailed time points.

4. ECOG performance status
5. Clinical laboratory tests (local and central laboratories) (Note: Lab data must be performed and reviewed before dosing)
6. Complete blood count (CBC) with differentials and D-dimer
7. Blood chemistry profile: fasting glucose, BUN, creatinine, alkaline phosphatase, ALT, AST, total bilirubin, total protein, albumin, globulin, sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, lactate dehydrogenase[16].
8. Urinalysis.
9. Serum sampling for pharmacokinetic studies *(for first cycle only)*
10. Infusion of IP
11. AE assessment

7.2.4. Infusion delays, missed doses and dose adjustment

7.2.4.1. Infusion delays and missed doses

Every effort should be made to schedule visits within the protocol-specified windows.

In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 3 days (including), the procedures at the original scheduled time point should be performed.

If the delay is more than 3 days, the procedures at the next infusion should be performed (the infusion at the original scheduled visit will be considered a missed dose).

Patients with infusion delays > 28 days should normally discontinue treatment and enter the Follow-up Period. If the Investigator intend to continue the treatment for patients who have infusion delay >28 days, specific consultation and agreement between the Investigator and the Medical Monitor are required in setting where benefit/risk may justify continued use of Investigational Product.

7.2.4.2. Dose modification for subsequent infusions

This study allows dose adjustment for toxicities. Dose modification is based on the toxicities from previous infusions. Patients who experience reversible DLTs **are** allowed to receive

[16] Any new Grade≥3 laboratory abnormality, such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medical Monitor should be contacted.

additional infusions at the next lower dose level, provided that the toxicities have reverted to grade≤1 in 28 days after last infusion, and that the patients still meet the inclusion criteria for adequate organ functions. Dose modification for reasons other than toxicities is not allowed, unless it is scientifically justifiable and must be agreed by the Sponsor.

For patients who experience DLTs, re-escalation to the dose level causing DLT is not permitted. Up to two dose-level reductions per patient are allowed in this study.

7.2.5. Discontinuation of patients from treatment

Each patient has the right to withdraw from the study any time. Patients MUST discontinue Investigational Product (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Withdrawal of informed consent (patient's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or inter-current illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Pregnancy or beginning breastfeeding
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Poor compliance with protocol.
- Discretion of the investigator.
- Disease progression or clinical deterioration that no further benefit from treatment is likely (clinical deterioration should be guided by clinical observation described in Section 6.2 and Investigator's judgment).
- Dosing delays longer than 28 days

All patients who discontinue should comply with protocol specified follow-up procedures as outlined in Section 7.2.5 . The only exception to this requirement is when a patient withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

7.2.6. Replacement of participants

A patient who is withdrawn from the study before the first 4 weeks after first infusion of IP may be replaced with a new one to receive the same dose level if the withdrawal from the study is not related to treatment-emergent toxicities.

7.3. Follow-up period

After completion of the Treatment period, the patients will have 6 monthly follow-up visits. All patients should complete Follow-up Visit 1 (28 ± 3 days after the last dose of IP).

The procedures for the follow-up visits are as follows:

1. Physical examination
2. Vital signs
3. ECOG performance status
4. AE assessment
5. 12-lead ECG
6. CBC with differentials and D-dimer
7. Coagulation profile: PT, INR, aPTT
8. Blood chemistry profile: fasting glucose, BUN, creatinine, alkaline phosphatase, ALT, AST, total bilirubin, total protein, albumin, globulin, sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, lactate dehydrogenase, IgG and IgM.
9. Thyroid function tests: TSH, T3 and free T4[17].
10. Urinalysis.
11. Urine pregnancy test for female patients with child-bearing potential[18]
12. Concomitant medications
13. Tumor assessment: if the prior imaging studies are done more than 8 weeks ago)
14. Pharmacokinetic and pharmacodynamic studies[19].

If the patient refuses or is unable to attend the follow-up visit 1, the reason(s) should be noted in the patient's source documentation.

[17] Every 8 weeks.
[18] A positive urine pregnancy test needs to be verified by a serum beta-HCG test. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child-bearing potential.

[19] Only for follow-up visit 1.

Completion of subsequent follow-up visits (Follow-up Visits 2 and beyond) will depend on the status of the patients at the end of treatment. Except for patients who discontinue due to worsening PD, all patients will be followed from the last dose of IP for approximately 6 months until relapse, initiation of a new therapy or the toxicities stabilized or ≤ grade 1. The evaluations performed during the Follow-up Visits will be recorded on the CRF.

Whether or not each patient completes the study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received. Patients will be considered to have completed Cycle 1 treatment if they completed 4 infusions of IP in Cycle 1 and completed all evaluations at the end of Cycle 1.

7.3.1. Survival follow up

Following completion of the treatment and follow-up periods, all patients will be followed for survival after completion of treatment phases and through the follow-up period of the protocol. Patients will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until study completion or termination by the Sponsor.

7.4. Post study access to Investigational Product

At the end of the protocol-specific periods of active study therapy, the Sponsor will not continue to supply study drugs to the patients/investigators unless the Sponsor decide to extend the study. The Investigator should ensure that the patients receives appropriate standard care to the condition under the study.

7.5. Records of concomitant medications and procedures

All medications, including pharmacologic doses of vitamins, herbal medicines, or other alternative medicine all transfusions, including blood component therapies, IV immunoglobulin, and hematopoietic growth factors administered within 28 days before first infusion are to be documented in the appropriate source documents and the CRF, along with the reason for and details of therapy use. Results of assessments must be reviewed by the safety review committee (SRC) before administering the first dose of the next cycle.

7.5.1. Prohibited concomitant medications and procedures

The following medications, therapies, and procedures are prohibited during the study:

- Any investigational agent other than HLX06.

- Any anti-neoplastic treatment with activity against epithelial cancer other than investigational product.
- Radiation therapy unless for pain relief at local lesion.
- Any surgery for the management of the patient's disease, unless for life-threatening situations during treatment period.
- Thrombopoietin-mimetics.
- Myeloid growth factors to stimulate faster granulocytic recovery, unless for neutropenic fever.
- Erythropoietic agent is not permitted, except for the management of patients with treatment-emergent renal failure or those with documented low erythropoietin.
- Non-steroidal anti-inflammatory drugs (NSAIDs), unless for pain relief.
- Live vaccines are NOT allowed during the study.

7.5.2. Permitted concomitant medications and procedures

Prophylactic pre-medications: Medications intended to prevent infusion reactions or other toxicities are permitted by previous experience with HLX06 in a patient as described in Section 6.4.

Corticosteroid use: Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the patient is on a stable dose. Non-absorbed intra-articular corticosteroid injections are permitted. Stable corticosteroid use with less than 10 mg prednisone is permitted.

Prophylactic antimicrobial agents: If the patient is considered to have high-risk for infection during the study period, prophylactic antimicrobial agents are allowed until the risk is lowered. Prophylactic antibiotics are to be provided according to institutional guidelines at the study center. If no institutional guidelines exist, prophylactic antimicrobial therapy (e.g., oral fluoroquinolone [levofloxacin or ciprofloxacin] for bacterial infections, oral fluconazole for fungal infections, and oral famciclovir 250 mg twice daily or equivalent for viral infections) are allowed for high-risk patients from the start of investigational product administration until the infection risk is lowered or recovery of white blood cells (WBCs).

Transfusion support: The use of blood components is recommended during the study period. Packed red blood cell (RBC) transfusion is recommended for hemoglobin ≤8.0 g/dL or per institutional guidelines. Platelet transfusion is recommended for platelet counts ≤20×109/L or with signs of bleeding or per institutional guidelines.

Palliative therapies: Palliative therapies (e.g. focal radiotherapy for pain, thoracentesis, or paracentesis for comfort may be administered after consultation with the Medical Monitor.

Vaccines: the use of killed or attenuated vaccines for the prevention of influenza is permitted at any time without a study drug washout interval. The use of other killed or attenuated vaccines for the prevention of infectious diseases may be permitted on a case-by-case basis and must be discussed with the Medical Monitor prior to its use. A washout interval prior to and post vaccination while on study may be required in these instances. Any vaccinations given while on study must be documented in the patient's medical records and in the CRF.

All patients should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the patient or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page. The addition of a new concomitant medication for which there is a concern that it may not be permitted should be first reviewed with the Medical Monitor.

No concomitant medication information will be collected following patient discontinuation from the study except for concomitant medication use associated with study drug-related adverse events or adverse events that lead to discontinuation from study.

7.5.3. Effective contraceptive measures

For female patients of child-bearing potential and male patients whose sexual partners are of child-bearing potential, patients should agree to use an effective method of contraception during the treatment period and for at least 180 days following the last dose of study drugs.

Effective contraceptive measures include: (a) intrauterine device plus one barrier method; (b) oral, implantable or injectable contraceptive plus one barrier method; or (c) tow barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (cream or gel that contain a chemical to kill sperms).

7.5.4. Treatment of isolated lesions.

Treatment of isolated/symptomatic lesions by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time beyond Cycle 2.

All interventions should be discussed in advance with the Medical Monitor.

7.6. Study participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason

for discontinuation. At the end of each cycle, the subject continuation status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation or deviation
- Disease progression
- Subject withdrew consent
- Subject is lost to follow-up
- Death
- Other unspecific reasons

8. EVALUATION OF SAFETY, IMMUNOGENICITY AND EFFICACY

8.1. Evaluation of safety and tolerability

The primary objective of this study intends to evaluate the safety and tolerability of IP. The following evaluations will be performed to measure the safety and tolerability:

Clinical laboratory tests (blood, urine sampling for clinical laboratory parameters), ECOG performance status, physical examinations including vital sign measurements, ECG, and the incidence and severity of treatment-emergent adverse events.

8.2. Immunogenicity

Immunogenicity refers to the development of an immune response to the HLX06 itself, and is characterized by the antibodies (ADA) that the patients may develop to react with HLX06. These may result in more rapid clearance of the IP from the bloodstream or predispose the patient to infusion reactions upon retreatment with IP at a later date. The ADA may also likely potentiate the drug effect by prolonging its half-life. Blood samples for immunogenicity analysis are mandatory and will be collected from all patients prior to every infusion of IP in Cycle 1 and before first infusion in subsequent 5 cycles or up to 18 weeks, whichever comes first and on the day of follow-up visit 1.

8.3. Efficacy evaluation

The efficacy parameters are the disease control rate (number of patients with CR/PR/SD divided by the total number of patients treated), and objective response rate (ORR) (number of patients with confirmed responses of CR or PR, divided by the total number of treated patients with measurable disease at baseline). Tumor response status will be assessed using RECIST 1

The response to treatment will be assessed in the following schedule:

1. For the first 24 weeks, treatment evaluation is conducted every 8 weeks (regardless of treatment delay).
2. After 24 weeks, treatment evaluation is conducted every 12 weeks

Tumor specific antigen levels (i.e. CEA, CA125, CA19-9, AFP, PSA for prostate cancer) are not used to confirm response, but they will be measured to provide ancillary support for disease response when appropriate in some tumor types.

Efficacy evaluation should use the same modalities. Repeat bone scan for metastatic bone disease is indicated based on clinical judgement by the Investigator.

9. PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATIONS

9.1. Pharmacokinetic studies

Pharmacokinetic study is mandatory for all patients in this study. Blood samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

For pharmacokinetic analysis of HLX06, blood samples of 5 mL were drawn pre-dose (within one hour before first infusion), after the end of infusion (within 30 minutes) and at 2, 4, 8 (±15 minutes allowable) hours as well as at 24, 48, 96, and 168 hours after the end of 1st and 4th infusion in Cycle 1. Additional time points include pre-dose and after the end of 2nd and 3rd infusions (within 30 minutes) in Cycle 1. Thereafter, the serum levels of HLX06 will be measured before the first infusion of Cycle 2 to Cycle 6 or up to 24 weeks, whichever comes first; and on the day of follow-up visit 1, whenever possible.

Blood samples will be processed to collect serum and stored at -70 degrees Celsius. Serum samples will be analyzed for HLX06 by a validated ELISA method.

Non-compartmental pharmacokinetic analysis will be used to estimate the PK parameters. The following parameters are determined from the serum concentration data of HLX06: maximum serum concentration (C_{max}), time to reach C_{max} (T_{max}), elimination rate constant (λ_z) , elimination half-life ($t_{1/2}$), area under the serum concentration-versus-time curve within one dosing interval ($AUC_{0\text{-}tau}$), area under the serum concentration-versus-time curve until infinity ($AUC_{0\text{-}inf}$), volume of distribution during terminal phase (V_z), and at steady state (V_{ss}), total body clearance from serum CL, and mean residence time (MRT). C_{max}, and T_{max} are taken directly from the plasma concentration curve, terminal half-life is determined from the terminal slope of the log-transformed plasma concentration curve using linear regression on terminal data points of the curve.

Concentrations below the lower limit of quantification, which are before the last quantifiable data point, are taken as zero for calculating the AUC. Pharmacokinetic results are presented only descriptively. No statistical tests are performed with pharmacokinetic parameters.

9.2. Pharmacodynamic study

This study also incorporates mandatory pharmacodynamic study by examining serum concentrations of VEGF-A, soluble VEGFR-1, soluble VEGFR-2. The sampling time points are pre-dose and after each infusion in cycle 1 in conjunction with pharmacokinetic studies.

10. ADVERSE EVENT REPORTING

10.1. Definitions of an adverse event and causality analysis

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 4.0 in this study.

If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate.

Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 4 and reported in the study report.

A laboratory abnormality is considered an adverse event if it results in any one of the following:

- discontinuation from study drug,
- necessitates therapeutic medical intervention,
- if the Investigator assesses the abnormality as an adverse event, or
- any laboratory test that is clinically significant or meets the definition of an SAE

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g. anemia versus low hemoglobin value). These adverse events

will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

The following is required for the description of each adverse event:

Description
Duration (start and end dates)
CTCAE Grade 1 through 5 or severity if CTCAE is not available
Relationship to the study drug - related or not related
Action(s) taken with study drug
Whether event was serious
Whether event is ongoing

10.2. Adverse event collection period

All protocol-related serious adverse events must be collected from the signing of the study specific informed consent until study drug administration.

All serious and non-serious adverse events reported from the time of study drug administration until 28 days following last infusion of study drug administration will be collected, whether elicited or spontaneously reported by the patient.

Serious adverse events occurring after the study-specific informed consent is signed but prior to the first dose of the investigational product will be collected only if they are considered by the investigator to be causally related to the study required procedures.

10.3. Relationship to study drug

The following is used to assess the relationship of the AE to the use of study results. Assessments are to be recorded on the appropriate CRF page.

Causality	Description
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and another cause of event is

Causality	Description
	equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly will be considered "associated." Events that are probably not or not related will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, it will consider the event associated.

Remedial Action(s) Taken

The remedial actions taken in response to an adverse event are to be recorded in the medical record. The options included but not limited to the following:

No action taken
Study drug permanently discontinued due to this adverse event
Study drug temporarily interrupted

10.4. Serious adverse events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

is fatal or life-threatening;
requires or prolongs hospitalization;
is significantly or permanently disabling or incapacitating;
constitutes a congenital anomaly or a birth defect; or
may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered serious adverse events:

Admission to a hospice for respite care;
Hospitalizations planned before entry into the clinical study;
Hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment;
Hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above);
Hospitalization as part of the normal treatment or monitoring of the studied indication;
Hospitalization to facilitate the work up of a ≤ Grade 2 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

10.5. Notification of serious adverse events

10.5.1. Reporting responsibility

Any serious adverse event occurring in a patient after he/she has provided informed consent, and while receiving study treatment must be reported. All patients who withdraw from the study should be monitored for at least 28 days following the last dose of IP for the occurrence of serious adverse events considered by the Investigator to be related to IP treatment. Patients should be contacted at least once within 28 days following the last dose of IP. Telephone contact is acceptable and should be within ±10 days of the 28-day time point. After 28 days following the last dose of IP, any serious adverse events considered by the Investigator to be related to IP treatment must also be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the IP has not yet been eliminated or the pharmacodynamic effects of the IP persist beyond 28 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a patient.

Each serious adverse event must be reported by the Investigator to the Medical Monitor or its, or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to IP. Serious adverse events occurring after 28 days from the last dose of IP must be reported if deemed related to IP. The report must include the adverse event term, patient identifier, attribution, description, concomitant medications used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to the Sponsor or its designee within 24 hours of receiving the information.

The Sponsor, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same IP that a serious adverse event has been reported.

10.5.2. Reporting procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to the Sponsor or its designee. The Medical Monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits. Follow-up information should also be sent to the Medical Monitor that receives the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the patient continued or permanently discontinued study participation. The form(s) and FAX confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event. The Sponsor or its designee will communicate serious adverse events to the study sites as required by local regulatory authorities.

10.5.3. Contact persons and numbers

The contact person and the phone/fax number are listed on the cover page of this protocol.

10.6. Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, the Sponsor considers an overdose, regardless of adverse outcome, as a serious adverse event in Section 10.4

10.7. Pregnancy

Pregnancy testing must be performed in all women with childbearing potential (WWCBP) throughout the study as specified in the Time and Event Schedule table, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All WWCBP must have a negative serum pregnancy test in the screening period and negative urine pregnancy tests during the study. If the pregnancy test is positive, the patient must not receive IP and must not continue in the study. The patient will be followed to determine the outcome of the pregnancy.

In addition, all WWCBP should be instructed to contact the Investigator immediately if they suspect that they might be pregnant (e.g., missed or late menstrual period) at any time in the study period or during the 28-day period following their last dose of study drug.

Male patients should contact the Investigator immediately if they suspect they may have fathered a child during the study or during the 28-day period following their last dose of study drug. When possible, such pregnancies should be followed (to term) to determine the outcome.

10.7.1. Reporting of pregnancy

Initial information on a pregnancy (during or after the study as defined above) must be reported immediately to Sponsor and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to the Sponsor or its designee according to Serious Adverse Event reporting procedures described in Section 10.4. A separated Pregnancy notification worksheet in Appendix 15.7 should also be filed to the Sponsor or its designee.

For female patients, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g., x-ray studies, CT scan). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

For male patients, follow-up information regarding the course of the partner's pregnancy, including perinatal and neonatal outcome should be reported when possible.

10.8. Rapid notification of adverse events of significance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events

(described in Section 10.5), even if the nature of the adverse event is not deemed serious:

Adverse events that potentially meet DLT criteria.
Adverse events that potentially meet the delayed DLT criteria.
Grade 3 or 4 infusion reactions whether or not the event is a DLT.

10.9. Other safety considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

11. DESCRIPTION OF STATISTICAL METHODS

11.1. Bayesian optimal interval design and sample size determination

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015) to find the MTD. The BOIN design is a novel Bayesian dose-finding method that optimizes patient ethics by minimizing the chance of exposing patients to sub-therapeutic and overly toxic doses. The BOIN design yields an average performance comparable to that of the continual reassessment method (CRM) in terms of selecting the MTD, but has a lower risk of assigning patients to sub-therapeutic or overly toxic doses (i.e., better patient ethics).

The target toxicity rate for the MTD is 0.3 and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 3. But in this study, there are two early stopping rules: (1) when the lowest dose level is eliminated due to toxicity and (2) when the new patient number at certain dose level reaches 15.

The dose escalation/de-escalation rules have been described in the Synopsis and tabulated in Table 1. The R codes used in the BOIN 2.4 package to derive the rules are listed in Section 15.5.

11.1.1. Determination of MTD

After the trial is completed, we determine the MTD based on the isotonic regression as specified in Yuan et al[5].The MTD will be determined by the number of patients with DLT in the first cycle and the total number of patients treated at certain dose level. The BOIN package in R will be used to estimate MTD. The determined MTD is the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate of 30%. If there are ties, we select the higher dose level when the isotonic estimate is lower than the target toxicity rate; and we select the lower dose level when the isotonic estimate is greater than the target toxicity rate.

11.1.2. Operating characteristics

The following table (Table 2) shows the operating characteristics of the proposed design for this trial with 6 scenarios defined by different DLT rates for 6 dose levels. These operating characteristics are based on 1000 simulations of the trial using the acceptable toxicity range [0.21, 0.39]. The operating characteristics show that the design selects the true MTD with high probabilities and allocate more patients to the dose levels with the DLT rate close to 0.3.

Table 2 Operating Characteristics of the BOIN design

Toxicity range		Dose level						Number of pts	% early stopping
		1	2	3	4	5	6		
	True DLT rate	0.05	0.10	**0.30**	0.45	0.60	0.8		
[0.21, 0.39]	Selection %	0.3	18.9	**58.5**	20.0	2.3	0	27.7	0.0
	# pts treated	3.6	7.2	**10.9**	5.2	0.8	0		
	True DLT rate	0.12	**0.30**	0.46	0.60	0.70	0.9		
[0.21, 0.39]	Selection %	21.2	**57.7**	19.0	1.7	0.2	0	25.1	0.2
	# pts treated	7.4	**11.2**	5.6	0.9	0.1	0		
	True DLT rate	0.26	**0.50**	0.65	0.75	0.80	0.9		
[0.21, 0.39]	Selection %	73.1	**18.2**	0.3	0	0		20.1	8.4
	# pts treated	12.4	**6.7**	0.9	0	0			
	True DLT rate	0.05	0.10	0.16	**0.30**	0.50	0.7		
[0.21, 0.39]	Selection %	0.2	2.7	23.7	**55.7**	17.1	0.6	29.2	0.0
	# pts treated	3.7	4.7	7.3	**9.1**	3.9	0.4		
	True DLT rate	0.02	0.03	0.05	0.12	**0.30**	0.45		
[0.21, 0.39]	Selection %	0	0.1	0.6	19.9	**55.7**	23.7	29.8	0.0
	# pts treated	3.2	3.4	3.8	6.7	**8.5**	4.3		
	True DLT rate	0.5	0.65	0.75	0.80	0.90	0.95		
[0.21, 0.39]	Selection %	35.8	0.5	0	0	0	0	11.3	63.7
	# pts treated	10	1.3	0	0	0			

11.1.3. Sensitivity analysis

To examine the robustness of the proposed BOIN design, we use the BOIN package in R to examine the sensitivity of BOIN design with respect to acceptable toxicity region. The following table shows the simulation results under narrower [0.24, 0.36] or wider toxicity region, while keeping the other simulation parameters unchanged.

We can see that the results are generally similar to those reported in Table 2.

Table 3. Sensitivity analysis of BOIN design using scenario 1 in Table 2

Toxicity range		Dose level						Number of pts	% early stopping
		1	2	3	4	5	6		
	True DLT rate	0.05	0.10	**0.30**	0.45	0.60	0.8		
[0.18, 0.36]	Selection %	0.6	18.1	**56.4**	23.2	1.7	0	29.2	0.0
	# pts treated	5	10.0	**9.8**	4.0	0.5	0		
	True DLT rate	0.05	0.10	**0.30**	0.45	0.6	0.8		

Toxicity range		Dose level						Number of pts	% early stopping
		1	2	3	4	5	6		
[0.18,0.42]	Selection %	0.9	20.5	**57.5**	19.6	1.5	0	25.1	0.2
	# pts treated	3.7	7.2	**10.8**	4.8	0.7	0		

11.2. Study population

11.2.1. All enrolled population

All patients who sign informed consent form will be included. Patient disposition will be tabulated using this data set.

11.2.2. All treated population

All patients who receive at least one infusion or any partial dose of Investigation Product. This population will be used for safety analyses and efficacy analyses.

11.2.3. Pharmacokinetic data set

All available concentration-time data from patients who receive Investigational Product will be reported. All available PK parameter values will be included in the PK data set and reported, but only patients with adequate PK profiles will be included in the summary statistics and statistical analysis.

11.2.4. Response evaluable data set

Response-evaluable patients will be defined as all subjects who receive at least one infusion of Investigational Product, have a baseline tumor assessment with measurable disease, and one of the following: (1) at least one on-treatment tumor evaluation, (2) clinical progression, or (3) death prior to the first one-treatment tumor evaluation.

11.2.5. Exploratory pharmacodynamic study

All patients who receive at least one infusion of Investigational Product and have at least one measure of specific marker will be included in the data set for that marker. All treated patients with at least one baseline measurement and at least one on-treatment measurement will be included for the PD assessments.

11.3. Statistical considerations

11.3.1. Demographics and baseline characteristics

The demographics and baseline characteristics of the patients including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical conditions will be summarized by dose levels using descriptive statistics.

11.3.2. Extent of exposure

The dose of Investigational product received by patients will be summarized by dose level. A by-patient listing of treatment exposure will be generated.

11.3.3. Concomitant medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Concomitant medications will be summarized. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study. A listing of concomitant medications by subject will be provided.

11.3.4. Efficacy

The primary efficacy parameter is the objective response rate: (ORR, umber of subjects with confirmed responses of CR or PR), divided by the total number of treated subjects with measurable disease at baseline). Tumor response status will be defined according to RECIST 1.1 (Appendix 15.4). To perform an evaluation of anti-tumor activity, BOR outcomes, ORR, and disease control rate (DCR: number of patients with CR, PR, or SD divided by the total number of treated patients with measurable disease at baseline) will be tabulated by overall frequency distribution. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using Kaplan-Meier methods; PFS will be similarly summarized. Listings of individual tumor measurements, tumor burden and % changes in tumor burden will be provided. Changes in tumor burden will be presented graphically for each disease type, e.g. by waterfall or other plots.

11.3.5. Safety evaluation

The following safety parameters will be evaluated:

11.3.5.1. Adverse events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient (To prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.)

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing or within 30 days of the last visit for screen failures. The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a system organ class and a preferred term for each adverse event. The number of subjects who experienced at least 1 adverse event, study drug related adverse event, severe (Grade≥ 3) adverse event, serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study, using the worst grade reported within a subject. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE Version 4.0), and additional grouping by severity and relationship to study drug. Individual listings of adverse events will be provided. DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

11.3.5.2. Physical examination

Abnormal findings in physical examinations will be recorded as adverse events or baseline medical history and will be included in the respective summaries.

11.3.5.3. Vital signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

11.3.5.4. ECG

12-lead ECG results will be summarized by dose level.

11.3.5.5. Clinical laboratory tests

Clinical laboratory test values outside the normal range will be flagged in the data listing. Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately. NCI CTCAE Version 4.0 Grade will be assigned to some of the laboratory parameters, which are included in CTCAE Version 4.0. Laboratory values will be listed. The laboratory values which are outside normal range will be flagged as H (above high normal limit), L (below lower normal limit), or A (abnormal) in the data listings. The NCI CTCAE Version 4.0 Grade will also be flagged in the data listings.

11.3.5.6. ECOG performance status

ECOG performance status will be summarized by dose level using descriptive statistics.

11.3.6. Immunogenicity

A listing will be provided of all available immunogenicity data. A listing of immunogenicity data from those subjects with at least one positive Human Anti-Human Antibody (HAHA) at any time point will be provided by dose regimen. The frequency of subjects with at least one positive HAHA assessment, frequency of subjects who develop HAHA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

11.3.7. Pharmacokinetic analysis

The pharmacokinetic parameters will be calculated and listed for each patient and treatment cycle, alone with summary statistics including arithmetic and geometric means; standard

deviation; minimum, maximum, and median values; and coefficients of variations. The PK data will also be displayed graphically, as appropriate. Exploratory analyses on the PK data and their relationship to PD, safety, and immunogenicity evaluation may be investigated. Pharmacokinetic concentrations from limited samples will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling.

11.3.8. Pharmacodynamic analysis

The PD data will be assessed descriptively whenever possible and by exploratory statistical the relationship between PK and PD will be explored and the strength of the relationship will be assessed, whenever possible, comparisons of both raw and relative-to-baseline data.

12. ETHICAL ASPECTS

12.1. Ethics and good clinical practice

This study must be carried out in compliance with the protocol and the requirement of Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines (ICH E6R1 and its addendum) or similar regulations published by local regulatory agencies (e.g. the GCP guidance published by Taiwan Food and Drug Administration or Chinese Food and Drug Administration, US Code of Federal Regulations, Title 21, Part 50[21CFR50], and Title 21, Part 312[21CFR312]).

The protocol and any amendments and the patient informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment). All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

12.2. Confidentiality of study patients

Investigators must assure that the privacy of patients, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to the Sponsor or its designee, patients will be identified by their initials, patient number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of the Sponsor, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

12.3. Institutional review board (IRB)/independent ethics committee (IEC)

Before implementing this study, the protocol, the proposed ICF, and other information provided to patients must be reviewed by an IRB/IEC. A signed and dated statement that the protocol,

and ICF, patient recruitment materials/process (eg, recruitment advertisements), and any other written information to be provided to patients have been approved by the IRB/IEC must be given to the Sponsor or its designee before study initiation. The name of the chairperson of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to or its designee along with the IRB approval. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

The Investigator or Sponsor or its designee should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to patients and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

12.4. Informed consent

Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks/benefits, and other critical issues regarding clinical studies in which they volunteer to participate.

The Investigators, or their designees, will explain to each patient (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of patient participation, alternative treatment options, potential risks and benefits involved, and any discomfort which may occur during the patient's participation in the study. Each patient will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical care or relationship with the treating physician and caring medical team.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. The Sponsor or its designee supplies a proposed ICF template that complies with regulatory requirements, includes all elements required by ICH, GCP and applicable local regulatory requirements, and is considered appropriate for the study. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Any changes to the proposed ICF suggested by the Investigator must be agreed to by the Sponsor or

its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the Study Monitor or its designee after IRB/IEC approval.

Investigator must:

Provide a copy of the consent form and written information about the study in the language in which the patient is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
Allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study.
Obtain an informed consent signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion.
Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the patients, prior to the beginning of the study, and after any revisions are completed for new information.
If informed consent is initially given by a patient's legally acceptable representative or legal guardian, and the patient subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the patient.
Revise the informed consent whenever important new information becomes available that is relevant to the patient's consent. The investigator, or a person designated by the Investigator, should fully inform the patient or the patient's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that the regulatory authorities have direct access to patient records.

Patients who meet the eligibility criteria but are unable to give their written consent (e.g., stroke patients) may only be enrolled in the study with the consent of a legally acceptable representative. The patient must also be informed about the nature of the study to the extent compatible with the patients' understanding, and should they become capable, personally sign and date the consent form as soon as possible.

The rights, safety, and well-being of the study patients are the most important considerations and should prevail over interests of science and society.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Protocol amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by the Sponsor before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, by the local regulatory authority. A copy of the written approval of the IRB/IEC must be given to the study monitor, or their designee. Examples of amendments requiring such approval are:

Increase in drug dosage or duration of exposure of patients, or any significant increase in the number of patients under study;
Significant change in the study design (e.g., addition or deletion of a control group, or rule of dose escalation or de-escalation);
Increase in the number of procedures to which patients are exposed; or
Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all patients in the study. If an immediate change to the protocol is deemed by the Investigator to be necessary and is implemented by him/her for safety reasons, the Sponsor should be notified and the IRB/IEC for the study site should be informed within 1 working day. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to: (1) IRB/IEC for review and approval/favorable opinion; (2) the Sponsor and (3) regulatory Authority(ies), if required by local regulations.

If an amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring

formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to: (1) changes in the staff used to monitor studies; (2) minor changes in the packaging or labeling of study drug.

13.2. Monitoring procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a representative from the Sponsor will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the study monitor, or its designee, will visit the site regularly to check the completeness and timely updates of patient records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the study monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, compliance of local regulations and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

Representatives of the Sponsor or its designee must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by assigned auditors from the Sponsor and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. The audit reports will be kept confidential.

The Investigator must notify the Sponsor or its designee promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor or its designee.

13.3. Investigator site training

The Sponsor or its designee will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details

and procedures electronic CRFs, study documentation, informed consent, and enrollment of women with child bearing potential and patients in vulnerable population.

13.4. Recording of data and retention of documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the patient's visit (except for the last visit of the last patient, which should be completed in a timely manner, preferably within 5 working days), so that the study monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to the Sponsor or its designee.

All entries to the CRF must be made clearly in black ball-point or ink pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. **Correction fluid must not be used.**

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The Investigator must maintain source documents for each patient in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the patient's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., and also a copy of the signed informed consent, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for the maximum period required to comply with national and international regulations, or institutional procedures, or for the period specified by the sponsor, whichever is longer.

The Sponsor will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. The investigator must contact the Sponsor or its designee prior to destroying any records associated with the study.

If the Investigator withdraws from the study (eg, relocation, retirement, conflict of interest), the records shall be transferred to a mutually agreed upon designee (eg, another Investigator, IRB). Notice of such transfer will be documented and given in writing to the Sponsor.

Essential documents include: (1) signed protocol and all amendments; (2) IRB/IEC approvals for the study protocol and all amendments; (3) all source documents and laboratory records; (4) CRF copies; (5) patients' ICF; (6) any other pertinent study documents.

13.5. Study drug record

It is the responsibility of the Investigator to ensure that a current disposition record of investigational product (those supplied by the Sponsor or its designee) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable local regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each patient, including unique patient identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor or its designee
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

13.6. Case report forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be documented.

For sites using the electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on

the SAE form and Pregnancy Notification worksheet, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an Investigator or sub-Investigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet the training requirements and must only access the electronic data capture tool using the assigned user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals, not authorized for the study.

13.7. Auditing procedures

In addition to the routine monitoring procedures, the Sponsor or its designee, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. The Sponsor, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform the Sponsor immediately that this request has been made.

13.8. Publication policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of the Sponsor. Authorship will be determined by mutual agreement. The arrangement of authorship is based on the contribution of the study by the Investigators. The principle of authorship of any publication resulting from this study is as follows: (International Committee of Medical Journal Editor, 2006)

- Authorship credit must be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article

or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors must meet conditions 1, 2, and 3.

- When a large, multicenter group has conducted the work, the group must identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors must qualify for authorship, and all those who qualify must be listed.
- Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by statisticians assigned by the Sponsor, and not by the Investigators themselves.

Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and the Sponsor.

The data collected during this study are confidential and proprietary to the Sponsor. Any publications or abstracts arising from this study require approval by the Sponsor prior to publication or presentation and must adhere to the publication requirements as set forth in the approved clinical trial agreement (CTA) and the protocol. All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the Sponsor at the earliest practicable time for review. Publication of any confidential or proprietary information of the IP should be approved for the proposed presentation or abstract and may delay publication for purposes of filing a patent application or other business arrangement.

The Sponsor must receive copies of any intended communication in advance of submission (at least 28 days for a journal submission and 14days for an abstract or oral presentation). The Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as representative personnel from the Sponsor.

13.9. Disclosure and confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by the Sponsor or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by the Sponsor (protocols, Investigators' Brochures, CRFs, and other materials) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study.

13.10. Discontinuation of study

The Sponsor reserves the right to discontinue any study for any reason at any time.

13.11. Data management

13.11.1. Data collection

Investigators must enter the information required by the protocol onto the CRFs that are printed on "no carbon required" paper. The study monitors or designees will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to the Sponsor, or its designee, with one copy retained at the study site.

If Electronic Data Capture (EDC) system is deployed, eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each patient will be forwarded to the study sites for record keeping at the study site closure.

13.11.2. Database management and quality control

The information entered into the database will be systematically checked by data management staff from the Sponsor, or its designee.

Obvious errors will be corrected by the personnel from the Sponsor, or its designee after verification with the Investigator. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the study site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Sponsor study team.

13.12. Compensation policy

The sponsor will take out insurance and will take other necessary measures to compensate patients in this study for adverse health outcomes which occur during the trial.

The informed consent information sheet will describe compensation which can be received during the clinical trial. However, this will not apply to anything resulting from an intentional act or the negligence of the medical institution or an intentional act or the gross negligence of the subject.

14. SCHEDULE OF ASSESSMENTS

Procedure	Screening	Cycle1				Cycle 2~6				Cycle 7 and after				Follow-up period
Days		**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	
Weeks	**-4 to 0**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
Informed consent	X													
Inclusion/exclusion criteria	X													
Medical history[1]	X													
Demographics	X													
Baseline conditions[2]	X													
Pathology review[3]	X													
AE assessment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	x
DLT evaluation[5]		X	X	X	X									
Efficacy assessment[6]		Assess every 8 weeks in the first 24 weeks and every 12 weeks thereafter												

[1] Medical history includes collection of prior medications administered to the patient during the Screening Period, prior and concurrent medical conditions, baseline signs and symptoms.
[2] Baseline condition includes vital signs, performance status, adverse events left from prior therapies, amount of hemoptysis.
[3] Pathology review includes confirmation of pathology, its mutation status[4] AE assessment includes the adverse events left from prior therapies, the AE occurs after signing informed consent, but before the 1st infusion of IP.
[4] AE assessment includes the adverse events left from prior therapies, the AE occurs after signing informed consent, but before the 1st infusion of IP.
[5] DLT defining period is the first 4 weeks after the start of treatment.
[6] Efficacy assessment is done every 8 weeks in the first 24 weeks, every 12 weeks thereafter.

Procedure	Screening	Cycle1				Cycle 2~6				Cycle 7 and after				Follow-up period
Days		**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	
Weeks	**-4 to 0**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
Survival status[7]														X
Treatment/Drug Administration														
Hospitalization for infusion and PK study		X			X									
HLX06 infusion		X	X	X	X	X	X	X	X	X	X	X	X	
Clinical procedures														
Vital signs/weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory procedures														
CBC w/ DC and D-dimer	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid profile[9]	X													
Urinalysis[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/PTT/INR	X	X				X				X				X
Tumor markers[11]	X	Every 8 weeks in the first 24 weeks and every 12 weeks thereafter												
Thyroid function tests[12]	X	Every 8 weeks in the first 24 weeks and every 12 weeks thereafter												x
Pregnancy test (serum HCG)	X													
Pregnancy test (urine HCG)		X				X				X				X

[7] Every three months by either phone or in direct contact after the completion of follow-up visits.
[8] The screening procedures include performance status, hematology panel, chemistry panel, coagulation, urinalysis, lipid profile, serum lipase and amylase, thyroid function tests (TSH, T3, free T4) need to be completed with 28 days prior to first infusion of HLX06. If the hematology panel, chemistry panel, coagulation, urinalysis, serum lipase and amylase thyroid function tests are completed within 7 days of first infusion, they do not need to be repeated. Hematology panel: CBC with differentials, D-dimers level. Blood chemistry panel: fasting glucose, blood urea nitrogen (BUN), creatinine, ALT, AST, total protein, albumin, globulin, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, lactate dehydrogenase (LDH), IgG and IgM. All the blood tests need to be performed in fasting state.
[9] Total cholesterol and triglyceride.
[10]Urinalysis panel: color, turbidity, specific gravity, pH, leukocyte, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, blood cells. If the urinalysis indicates significant proteinuria (> 30 mg or >=2+ by urine dipstick), urinalysis must be repeated. If the repeat dipstick protein value is >30 mg or >= 2+ by urine dipstick, 24-hour urine collection is required to calculate total protein.
[11] Tumor markers include CEA, CA199, CA125, CA153, AFP and PSA. PSA is only indicated for patients with prostate cancer. These should be done every 8 weeks in the first 24 weeks, and every 12 weeks thereafter.
[12] Thyroid function tests include TSH, T3, free T4. They are done at Screening, every 8 weeks in the first 24 weeks, and every 12 weeks thereafter.

Procedure	Screening	Cycle1				Cycle 2~6				Cycle 7 and after				Follow-up period
Days		**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	
Weeks	**-4 to 0**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
HBsAg, HBcAb, and anti-HCV	X													
Serum lipase and amylase	X													
PK study[13]		X	X	X	X	X								X
Immunogenicity study[14]		X	X	X	X	X								X
Optional PD study[15]		X	X	X	X									
Imaging procedures														
12-lead ECG[16]	X	X				X				x				X
Cardiac ultrasound	X													
Chest X-Ray	X													
Tumor assessment CT/MRI imaging	X	Every 8 weeks in the first 24 weeks and every 12 weeks thereafter												X
Brain CT/MRI	X													
Bone scan	X	Repeat bone scan for metastatic bone disease is indicated based on clinical judgement by the Investigator												

[13] Pharmacokinetic analysis of HLX06: blood samples of 5 mL were drawn within one hour before and at the end of infusion, 2, 4, 8 (±15 minutes allowable) hours as well as at 24, 48, 96, and 168 hours after the start of 1st and 4th infusion in Cycle 1. Additional time points include before and after 2nd and 3rd infusions in Cycle 1. Thereafter, the serum levels of HLX06 will be measured before the first infusion of Cycle 2 to Cycle 6 or up to 24 weeks, whichever comes first; and on the day follow-up visit 1, whenever possible.
[14] Blood samples for immunogenicity will be collected from all patients prior to every infusion of IP in Cycle 1 and before first infusion in subsequent 5 cycles or up to 18 weeks, whichever comes first; and on the day of follow-up visit 1.
[15] The sampling time points are predose and after each infusion (within 30 minutes) in cycle 1 in conjunction with pharmacokinetic studies.
[16] At screening, predose and after the end of 1st infusion (within 30 minutes) of each cycle and on the day of follow-up visit 1.

15. APPENDICES

15.1. ECOG performance status

Table 4. Grading and description of ECOG PS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

15.2. Child-Pugh scoring table for estimation of liver reserve

Score	1	2	3
Encephalopathy	None	Mild	Marked
Ascites	None	Mild to moderate	Severe
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/mL)	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged or	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

Score	Description	Points
A	Mild; well-compensated	5-6
B	Moderate; significant functional compromise	7-9
C	Severe; decompensated	10-15

15.3. Adverse event severity scoring system

Table 5. Grading and Description of AE

Grade	Standard Adverse Event Severity Scoring System	
1	MILD	Aware of sign or symptom, but easily tolerated
2	MODERATE:	Discomfort enough to cause interference with usual activity
3	SEVERE:	Incapacitating, with inability to work or do usual activity
4	LIFE-THREATENING:	Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event.
5	FATAL	

15.4. RECIST criteria 1.1

Solid tumor response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST criteria[25]. Each category (measurable and non-measurable lesions) will be assessed and reported independently.

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-Target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment timepoint. The smallest sum of the longest diameters recorded since baseline will be used as reference when evaluating for progression. All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline.

Measurement of these lesions is not required, but the presence, absence, or worsening of each should be documented throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met.

Overall time point responses for all possible combinations of responses in target and non-target lesions with or without the appearance of new lesion.

Table 6. Classification of responses

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no*	PD
Any	PD	Yes or no*	PD
Any	Any	Yes*	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR: complete response; PR: partial response SD: stable disease; PD: progressive response; UE: unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to = determine the status of that particular tumor for that time point); NA: not applicable;(no target or nontarget lesions identified at baseline); ND: not done (scans not performed at this timepoint)

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having "symptomatic deterioration."

Table 7. Definition of lesions and imaging modality and their requirement

Definitions	Description
Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques, or as ≥10 mm with spiral (helical) computed tomography (CT) scan or two (2) times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Non-measurable lesions	Non-target lesions not classified as measurable lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and truly non-measurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	All measurable lesions up to a maximum of 5 lesions and 2 lesions per organ, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted.

Definitions	Description
	Longest diameter for target lesions - The sum of the longest diameter for all target lesions (SLD). **Complete response** - Disappearance of all target lesions. **Partial response**: At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. **Stable disease**: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. **Progressive disease:** At least a 20% increase in the sum of the longest diameters of target lesions (with addition of diameters of any newly emergent measurable lesions), taking as reference the smallest sum of the longest diameters (nadir) recorded since screening. UE/ND/NA
Non-target lesions	All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted. **Complete response:** Disappearance of all non-target lesions. **Incomplete response/stable disease**: Persistence of one or more non-target lesion(s). **Progressive disease**: Unequivocal progression of a non-target lesion or appearance of 1 or more new lesions.

Definitions	Description
	UE/ND/NA
Best overall response	The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.
Methods of measurements	The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.
Clinical examination	Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.
Chest X-ray	Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If patients with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or

Definitions	Description
	involving the mediastinum, are not suitable for measurements by chest x-ray.
Computed Tomography and Magnetic Resonance Imaging	CT is the primary imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm. In patients in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated the best effect. All images from each examination are to be included and not selected" images of the apparent lesion.

Definitions	Description
	All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination. When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

15.6. R codes used to derive the dose escalation and de-escalation

Table 1 is generated with software R 3.4 with BOIN package 2.4. Various scenarios of toxicity distribution with target toxicity rate at different dose levels are generated with dfcrm package.

Operative characteristics of the study design are also generated with BOIN package.

The R script for this study is as follows:

```
if(!require("pacman")){
install.packages("pacman")}
pacman::p_load(BOIN, dfcrm)
target<-0.3 # target toxicity rate#
nc<-10 #number of cohorts
cs<-3 # cohort size
nes<- 15 # number of pts in a cohort for early stop#
sb<-target*0.7 #set up the safe boundary, narrower than default#
tb<-target*1.3 #set up the toxic boundary,narrower than default#
get.boundary(target=target,ncohort=nc, cohortsize = cs, n.earlystop = nes, p.saf =sb, p.tox = tb, extrasafe = FALSE, offset = 0.05)
# get operating characteristics
# use dfcrm to get priors
delta<-0.09 # the acceptable range of DLT
mtd0<-3 # prior MTD, usu. the starting dose#
k<-6 # number of dose levels
p0<-getprior(halfwidth=delta, target=target, nu=mtd0, nlevel=k, model = "empiric")
p1<-round(p0, digits = 2)
p1 # the toxicity probability distribution
get.oc(target = target, p.true = p1, ncohort = nc, cohortsize = cs, n.earlystop = nes, p.saf = sb, p.tox = tb, extrasafe = FALSE, ntrial = 1000) # get operative characteristic
```

15.8. Pregnancy notification worksheet

Study No. HLX06FIH	Site No.:	Patient ID No.	Patient Initial

Did the patient withdraw from the Study? Yes____. No._____

Sex	SEX Code: ( ) Female patient ( ) Male patient partner

Estimated Date of Conception								
Day		Month			Year			

Investigational Product Administration Starting Date								
Day		Month			Year			

Investigational Product Administration Stop Date								
Day		Month			Year			
FAX to: Henlix Biotech Co. Ltd, Attn: Shufan Lin FAX NO. +886-2-27927901 TEL: +886-2-27927901								
Day		Month			Year			

Investigator Name:	Tel:
Institution:	Site No.:
Address:	

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