SUMMARY OF CHANGES -- Consent

Protocol #:HLX06FIH
Protocol Version Date: Version 1.0 2017-Jun-13
Approval Date: 2017-Nov-07 by TMU-Joint Institutional Review Board

Protocol Title: A PHASE 1 FIRST-IN-HUMAN DOSE ESCALATION 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

Informed Consent Version Date: 2017-Jun-13

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Consent Form

Study Title for Study Participants: Testing the new anti-VEGFR2 antibody HLX06 in patients with advanced cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

A phase-1 first-in-human dose escalation 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.

INTRODUCTION

You are being asked to take part in this clinical research study because you have an advanced or metastatic solid tumor that has not responded to previous treatment. It is your choice whether to take part in the study. You may decide that you do not wish to participate.

Please take time to read the following information carefully. Please also discuss it with friends, relatives, and your family doctor if you wish.

If you decide not to take part in this study, the standard of treatment you receive now or in the future will not be affected in any way. If you decide to take part, your doctor and/or the research staff will explain this study to you in further detail and you will be asked to sign this form. You are free to withdraw from this study at any time. Your standard practice of care would not be affected in any way if you were to withdraw. If you withdraw, you will not receive further treatment with the study drug.

The study is under the direction of Dr. _____. Please ask your doctor or the study staff to explain any words or information that you do not fully understand.

NATURE AND PURPOSE OF THE STUDY

Why is this study being done?

The purpose of this study is to test the safety and effect of an investigational drug called HLX06. An investigational drug means that it is a drug that is not Food and Drug Administration (FDA) approved for use outside of research studies. HLX06 is a humanized recombinant monoclonal antibody that targets VEGFR2. VEGFR2, the short name of **V**ascular **E**ndothelial **G**rowth **F**actor **R**eceptor-2, is a protein that can be found on the cells lining inside of blood vessles and also on the surface of many cancer cells. HLX06 is modified to bind the VEGFR2. VEGFR2 is thought to play some role in a process called angiogenesis (growth of blood vessels). Angiogenesis is considered to play an important role for the growth of cancer because the growth of blood vessels are needed to supply the nutrition needed tumor growth. One drug called Cyramza, which also targets the same VEGFR2, is available to treat different types of cancer, such as stomach cancer, bowel cancer and lung cancer after a patient has failed standard chemotherapy.

The company which makes HLX06 wants to find out in this study:

- The maximum tolerated dose (the highest and safe dose for the patients) of HLX06
- What effects HLX06 has on your body.
- The amount of HLX06 in your body at different times.
- What effect (good or bad) HLX06 has on your cancer.

How many people will take part in the study?

A maximum of 30 patients are expected to take part in the study. The patients who take part in this study will be enrolled in groups called cohorts. Each cohort will have from one to three patients. Patients will be enrolled until the point that the maximum tolerated dose is determined. If you are having a positive benefit from treatment with HLX06, you can continue to receive treatment with the study drug until the maximum of one year or withdrawal from the study, whether or not the study has reached the maximum tolerated dose.

STUDY PROCEDURES

How long will I be in this study?

You will receive the HLX06 injection once a week until any one of the following conditions is met

- You decide not to participate this study for any reason.
- This drug no longer works on your disease.
- You have new medical issues that prevent you from receiving more of this drug.
- You have unacceptable side effects caused by the drug. You can no longer follow the required procedures or requirements of this study.
- Your doctor decides that your condition does not allow you to receive more of this drug.
- You miss the scheduled infusions for 4 weeks because you cannot keep up with the weekly visits.
- You become pregnant.

After your withdrawal from the study, you doctor will require you to complete the examinations as required by the study. He or she may also continue to monitor you for side effects for up to 16 weeks.

The length of participation in this study will vary for each person and will be determined by the number of treatment cycles you receive. You are expected to be in the study for at least 3 to 6 months or longer.

Your treatment with the study drug will continue if you receive benefit from the study drug, until you have an unacceptable side effects to the drug or your cancer gets worse, or you decide not to keep on treatment for any reason, or you have received the drug for one year.

What extra tests and procedures will I have if I take part in this study?

Most of the examinations, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra procedures like blood draws and additional tests to make sure your condition is suitable to take part in this study.

What happens before the treatment

You will need to have the following extra procedures to determine if you can take part in the study. The required tests or procedures are listed below.

- Detailed medical history and physical examination.
- Vital signs (body temperature, heart rate, respiratory rate and blood pressure), body weight and height.
- Baseline condition assessment
- Documentation of disease assessment
- Documentation of measureable diseases.
- History of past treatments and any toxicity relating to past treatment that is still left on you.
- Review of pathology reports and any known mutations in your cancer cells(Note: the information of different mutations needs to be documented. The presence and types of mutations are not essential to take part in the study, however).
- Complete blood count (CBC) with differentials (these tests measure whether you have

enough blood cells in your body), and D-dimer.

- Coagulation tests (these tests measure how fast your blood clot): prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR).
- Blood chemistry tests (these tests measure how well your body organs function), including: Fasting glucose, alkaline phosphatase, ALT, AST, total bilirubin, magnesium, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, globulin, potassium, sodium, chloride, uric acid, lactate dehydrogenase (LDH), total cholesterol, triglyceride.
- Thyroid function tests (these tests meaure how well your thyroid gland functions): thyroid-stimulating hormone (TSH), free thyroxine (FT4)
- Serum lipase and amylase (these tests measure the key digestive enzymes to help your body break down fat and starch)
- Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), Hepatitis C antibody (anti-HCV).
- Urine tests.
- Tumor markers (CEA, CA199, CA125, CA153, alpha-fetoprotein and prostate surface antigen if you have prostate cancer)
- Urine pregnancy test.
- CT scans with contrast (chest, abdomen and pelvis) for tumor assessment (if the scans are taken less than 6 weeks before the first injection of the study drug, you do not need to repeat the scans). The addition of contrast medium is to make the scans more accurate to detect the changes of your cancer in your body.
- Brain MRI scans with contrast (if the scans are less than 6 weeks before the first injection of study drug, no need to repeat the test). The addition of contrast medium is to make the scans more accurate to detect the changes of your cancer in your brain.
- 12-lead electrocardiogram (ECG) to examine your heart function.
- Heart ultrasound
- Bone scan (if your doctor thinks it is necessary for your disease).
- X-ray, CT or MRI if your bone scan is abnormal and your doctor needs to make sure your condition.

After these procedures, if your doctor determines that it is not suitable for you to take part in the trial, then you cannot take part in the trial.

Additionally, your signature on this consent form is required prior to your initiation of study treatments.

What happens during the treatment?

Before you receive your first injection of the HLX07 drug, your doctor will order a blood test again to make your condition is suitable to receive the drug.

After you receive your first dose of HLX06, which lasts two hours, the followings will occur:

- Your doctor and nurse will keep monitoring your condition.
- Your blood will be drawn for routine blood tests. Additional blood samples (approximately 1 teaspoon each time) will be drawn 1, 2, 4, 8, 24, 48, 96, and 168 hours after the injection of this drug.
- You will stay in the hospital for at least one day to be monitored for any side effects

If you do not experience serious toxicities, the following will occur:

- You will be given the second shot of the drug at the same dose once every week.
- Your blood will be drawn for routine tests and for measurement of the drug levels in your blood.
- In the fourth week, your blood samples (approximately 1 teaspoon each time) will be drawn 1, 2, 4, 8, 24, 48, 96, and 168 hours after the injection of this drug.

- Your doctor will order tests to examine the effect of the drug to your cancer every 8 weeks until the study drug no longer works on you.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information.

Neither you nor your health care plan/insurance carrier will be billed for collection of all of the samples that will be used for this study.

Because the tests using your stored blood samples will not be available while you take part in this study, you or your doctors will not have access to the results of these tests. These tests will not affect your treatment, either. You will NOT be informed once the test results are available because these tests are investigational and the exact meaning of the results will not be able to be confirmed.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there are risks that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
- You may be asked sensitive or private questions which you normally do not discuss.

The antibody drug used in this study may affect the function of other organs, such as liver, kidneys, heart, and blood. The study doctor will be testing your blood and will inform you if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug and the study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers expect from Cyramza because Cyramza and HLX06 share similar mode of action on human cells. There might be other side effects that researchers do not yet know. If new side effects are found, the study doctor will discuss them with you.

HLX06 has not been used in humans before. However, based on its mode of action and the studies in monkeys, its toxicities are expected to be similar to Cyramza. The common and possible side effects are listed in the following tables.

Common side effects
• Back pain or spasm • Blurred vision • Burning, crawling, itching, numbness, prickling, "pin and needles", or tingling feelings • Chest pain • Chills • Confusion • Convulsions • Decreased urine output • Dizziness, faintness, or lightheadness when getting up suddenly from a lying or sitting position • Fainting • Fast, pounding or irregular heartbeat or pulse • Feeling of warmth • High blood pressure • Diarrhea • Headahce

Potentially serious side effects
• Severe infusion related reactions • Severe bleeding or coughing up blood • Temporary blindness. • Bowel performation • Paralysis • Severe headache • Impaired wound healing

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drug used in this study could be very damaging to an unborn baby. You should use barrier contraceptive method (e.g. condom) to prevent pregnancy while in this study.

What possible benefits can I expect from taking part in this study?

This is the first time for this drug to be used in human beings. The potential benefits for you and your cancer are unknown.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will discuss with you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may discharge you from the study for the following reasons:

- This drug no longer works on you.
- You have new problems that prevent you from receiving more of this drug.
- You have unacceptable side effects.
- You decide not to participate in this study.
- You can no longer follow the required procedures or requirement in this study.
- Your doctor thinks your condition does not allow you to receive more of this drug.
- You miss the scheduled infusions for four weeks in a row because you cannot keep up with the weekly visits.
- You become pregnant.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The drug, HLX06, will be supplied at no cost to you while you take part in this study. It is possible that HLX06 may not continue to be supplied after you have received the drug for one year. If this occurs, your study doctor will discuss with you about your options and also discuss with the Sponsor whether it is beneficial to keep treating you without the possibility of hurting you in the long term.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while on this study, including the cost of tests, procedures, or medicines to manage any side

effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please inform your study doctor immediately. The study sponsor will offer to pay for medical treatment for injury related to this drug. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs not related to this study drug.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this, even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration in the U.S., and similar institutions if other countries are involved in the study.

Where can I get more information?

You may call Henlix Inc. to get the same information about studies at: _____.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ (insert name of study doctor[s]) at _____ (insert telephone number).

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____