patient's initials☐☐☐ random number☐☐☐

Informed consent

Dear Gentlemen:

We cordially invite you to participate in A Phase III Randomized, Double-blind, Placebo-controlled, Cross-over Study to Evaluate Olanzapine Combined with Fosaprepitant, Ondansetron, and Dexamethasone for Preventing Nausea and Vomiting in Patients with Testicular Cancer Receiving 5-day Cisplatin Combination Chemotherapy, please read the following information carefully before deciding whether to participate in this study.

1、Background

Although testicular cancer is rare, accounting for only 1 % of all cancers in males, it is the most common solid tumor among young men in the 20–39 years old. Since the introduction of cisplatin-based chemotherapy in the 1970s, the prognosis of patients with testicular cancer has been dramatically improved, with a 10-year relative survival approaching 95%. However, treatment-related complications, including acute and long-term toxicities remain unsolved.

Cisplatin is a chemotherapy agent with the highest emetic. The risk of emetic is more than 90% when the daily dose of cisplatin is ≥50mg/m^2. While the standard dose of cisplatin is as high as 100mg/m2 in five consecutive days for testicular cancer. Early data showed that patients with germ cell tumor who received multi-day cisplatin chemotherapy experienced vomiting for more than 10 times on the first day and lasted for several days [2]. Severe nausea and vomiting could reduce dietary intake, cause or aggravate other toxicities, such as fatigue, neutropenia, anemia, and finally might interfere with implementation of chemotherapy and anti-tumor efficacy. Therefore, chemotherapy-induced nausea and vomiting (CINV) is one of the most feared side effects experienced by patients with testicular cancer.

The mechanism of CINV has been elucidated in the past decades. The vomiting center is pathological located in the side of the medulla oblongata reticular structure, which directly controls the occurrence of vomiting. Chemotherapeutic drugs can induce the release of a variety of neurotransmitters which bind of their receptors and play an important role in the formation of vomiting. The neurotransmitters associated with CINV include 5-hydroxytryptamine (5-HT), substance P/neurokinin -1 (NK-1), cannabinoid, dopamine, acetylcholine, and histamine. According to the time of vomiting, CINV can be divided

into three categories [2-3]: ① Acute nausea and vomiting: nausea and vomiting occurring within 24 hours after chemotherapy. This type of nausea and vomiting is often severe and is mediated by serotonin 3 (5-HT3). In addition, the binding of substance P to its specific receptor NK-1 also plays an important role in acute vomiting. ② Delayed nausea and vomiting: nausea and vomiting 24 hours after the administration of chemotherapy drugs, sometimes lasting for 5-7 days. Delayed CINV may be mediated by various mechanisms, and the main transmitter is substance P.③ Anticipatory nausea and vomiting: caused by conditioned reflex. It occurs when patients see chemotherapy drugs or other things related to chemotherapy. Anticipatory nausea and vomiting is mainly related to spiritual and psychological factors, and caused by poor control of acute nausea and vomiting.

Prophylactic medication is the key to control CINV. At present, there are three kinds of drugs widely used in clinical practice: ① 5-HT3 receptor antagonists, which specifically block the binding of 5-HT3 and its receptor, mainly controlling acute nausea and vomiting.② NK-1 receptor antagonist, blocking the binding of substance P to its receptor, has an inhibitory effect both on acute and delayed nausea and vomiting.③ The antiemetic mechanism of dexamethasone is still unknown, but its efficacy in the prevention of acute and delayed vomiting has been widely confirmed, and it has been used as a basic drug for the prevention of CINV. A number of large phase 3 randomized controlled studies and meta-analyses have confirmed that the combined use of 5-HT3 receptor antagonist, NK-1 receptor antagonist and dexamethasone could significantly reduce the occurrence of CINV induced by highly emetogenic chemotherapeutic drugs represented by single-day high dose cisplatin, with the control rate of vomiting is approaching 90%[3, 4].Therefore, this three-drug combination regimen has been recommended by several international and domestic guidelines such as NCCN/ESMO/ MASCC /CSCO for the prevention of highly emetogenic chemotherapeutic drug-associated CINV. For patients undergoing multiple days of highly emetogenic chemotherapy, current guidelines still recommend the use of the triple prophylaxis regimen based on the results of single-day chemotherapy studies. However, this recommendation is not supported by sufficient evidence-based medical evidence. A few small phase II studies have been conducted on CINV associated with multi-day hyperemetogenic chemotherapy. The only one small sample-sized phase III trial demonstrated the efficacy of the triplet combination of NK 1 receptor antagonist,5-HT3 antagonists, and dexamethasone in testicular cancer patients who were treated with 5-day cisplatin combination chemotherapy. Among 71 patients enrolled, 69 could be evaluated. The complete remission rate of vomiting was 42% for patients treated with the triple

antiemetic regimen, compared with 13% for patients treated with two drugs combination of 5-HT3 antagonists and dexamethasone [5]. Even if, 42% of overall vomiting control rate is significantly lower than 90% in patients receiving single-day chemotherapy. Moreover, prevention of nausea was extremely poor, and the overall control rate in was only about 25% even for patients treated with the triplet combination [5-7]. Finding a more effective regimen to prevent or reduce CINV for testicular cancer patients receiving 5-day cisplatin combination chemotherapy is urgently needed.

At present, several NK-1 receptor antagonists have been successfully developed and approved for marketing. Aprepitant, the first oral NK1 receptor blocker approved for clinical use, was launched in the United States in March 2003 and entered the Chinese market in September 2013. Fosaprepitant is the prodrug of aprepitan. In humans, fosaprepitant can be rapidly converted to aprepitan within 30 minutes after the end of intravenous administration of fosaprepitant, so its clinical efficacy is mainly attributed to aprepitan. A randomized, parallel, double-blind, positive-controlled trial demonstrated that fosaprepitant 0.15g intravenously (n=1147) had similar efficacy with aprepitan capsules 3 days orally (n=1175) in patients receiving cisplatin ≥70mg/m2. Fosaprepitant was well tolerated [8]. The most commonly reported adverse reactions in clinical studies included headache and injection site symptoms.

Olanzapine is the second generation of atypical neuroleptics, which is mainly used in the treatment of schizophrenia. Olanzapine antagonizes various vomit-related neurotransmitter receptors, such as dopamine receptor, 5-HT2 receptor, and histamine receptor, and has significant nausea and vomiting prevention effect. Accumulating evidences support the efficacy of olanzapine for prophylaxis of CINV for highly emetogenic chemotherapy. However, most studies focus on solid malignancies and single-day regimens. Moreover, the standard dose of olanzapine (10 mg qd) is associated with high risk of sedation, drowsiness, and fatigue. Subsequent studies showed that lowering olanzapine dose to 5mg per day had similar prophylactic effects on nausea and vomiting compared with 10mg, and significantly reduced the incidence of excessive sedation and drowsiness [9]. Therefore, many researchers suggest that 5mg of olanzapine per day may be a more predictive dose for nausea and vomiting. To improve antiemetic therapies for testicular patients receiving 5-day cisplatin chemotherapy, the current study aims to explore the efficacy and safety of low-dose olanzapine combined with nK-1 receptor antagonist (fosaprepitant), 5-HT3 receptor antagonist (ondansetron) and dexamethasone quadruplex antiemetics regimen.

2、Design of this trial

This study is a randomized, double-blind, placebo-controlled, phase III clinical trial. The study plans to enroll 75 patients. A crossover design method is adopted. Subjects were selected as their own control group, and the treatment sequence was randomly assigned. The two treatment sequence groups (olanzapine-placebo group and placebo-olanzapine group) were uniformly numbered and randomly assigned to the two treatment sequence groups in a 1:1 ratio. Neither you nor the study doctor can choose which treatment group you will be assigned to, nor do you and the doctor know what treatment you are receiving, and if your safety is at risk and your doctor judges you need to know what treatment you are receiving, Your doctor can find out which regimen you are receiving and plan how to manage it accordingly. Efficacy and safety evaluations will be conducted simultaneously during the treatment period.

Prophylactic antiemetic regimen:

Eligible enrolled patients will be randomized to receive olanzapine-placebo or placebo-olanzapine plus triple regimens of prophylactic antiemetic therapy during the first 2 courses of chemotherapy. The specific regimens are as follows:

Placebo group (control group)

Ondansetron: 8mg IV D1-5 30 minutes before chemotherapy;

Dexamethasone: 6mg Po d1-7;

Fosaprepitant: 150mg IVD D1, D4 60 minutes before chemotherapy;

Placebo: 5mg po d1-7

Olanzapine group (control group)

Ondansetron: 8mg IV D1-5 30 minutes before chemotherapy;

Dexamethasone: 6mg Po d1-7;

Fosaprepitant: 150mg IVD D1, D4 60 minutes before chemotherapy;

Olanzapine: 5mg Po D1-7

During the study and visit, if you develop severe nausea and vomiting, your study

doctor will administer rescue antiemetic treatment.

3、 Research plan

If you agree to participate in the study, and you sign an informed consent form, you will enter the "screening" period of the study. In order to determine whether it is safe for you to participate in the study, and to see if you are suitable to participate in the study, the researcher will ask you about information about your health history and current health, and you will also undergo some screening and screening procedures. Certain screening tests and procedures are part of your cancer treatment routine and may be required even if you are not participating in research studies. Other checks will only be done while you are participating in this study.

You will then be randomly assigned to a control group (placebo) and an experimental group. You will receive 5 days of chemotherapy and 7 days of antiemetic therapy. Your antiemetic effectiveness will be assessed from the start of your chemotherapy drug infusion (0 hours on day 1) to day 10 (approximately 240 hours total) based on the diary you fill out. We will collect information about each time you have nausea and/or vomiting and information about the medications you take. You should report the onset of vomiting, the use of remedies and the assessment of daily nausea within the first 24 hours from day 2 to 11 after treatment, as well as the time and date of any vomiting or retching attacks, as well as the use of rescue drugs. On days 2 to 11, you will need to use a visual analogue scale (VAS) to record your nausea rating within the previous 24 hours. Immediately after completing the diary on day 11, you will need to complete the Days 1-10 Functional Living Index - Emesis (FLIE) and Hospital Anxiety and Depression (HAD) questionnaires. During the study, you may receive "rescue therapy" for nausea or vomiting, however, after receiving rescue therapy, you will need to continue to receive study medication and complete the diary as instructed.

At any stage, it is important to tell your study doctor right away if your health changes significantly between visits, or if you have any concerns about the study. If you go to

other doctors, nurses, medical personnel for medical activities, you should tell them that you are participating in this study and that they can contact your study doctor for information. If you are hospitalized between study visits, it is important that you inform your study doctor as soon as possible.

4、Precautions:

- In most cases, treatment and testing will be done as routinely specified in the study protocol, but additional testing will be done at any time if deemed necessary by your doctor.
- If you are participating in a study, follow your doctor's arrangements for treatment. Tell your doctor promptly if you feel any discomfort or experience any adverse reactions. If your doctor decides to stop study treatment, your doctor will discuss your next steps with you.

5、Other things that require your cooperation:

During the research period, please follow the instructions of the research doctor to take medication, and come to the hospital for examination and visit at the agreed time. The examination includes vital signs, physical examination, blood routine, blood biochemistry, 15-lead electrocardiogram, etc. Completion of the ECOG Performance Status Scale, FLIE and HAD questionnaires, recording of episodes of vomiting or retching, use of rescue therapy, and daily assessment of nausea (VAS Scale for Nausea) in the patient diary.

Blood collection for exploratory research: Before the first chemotherapy, we will collect an additional 10ml of your venous baseline blood sample to measure the concentration of substance P and 5-HT in plasma. For this blood collection, we will give you a certain nutritional subsidy, subsidy See "Research Fees" for details.

During the study period (1) CYP3A4 substrates: terfenadine, cisapride, astemizole, amifostine, pimozide, etc.; (2) CYP3A4 inducers: phenytoin, carbamazepine,

barbiturates, rifampicin, rifabutin, Hypericum perforatum, etc.; (3) CYP3A4 strong inhibitors: clarithromycin, itraconazole, ketoconazole, etc.; (4) Chinese medicine or Chinese patent medicine. Medications that have been assessed by the study physician for use are excluded.

6、Risks and Discomfort:

Adverse effects of drugs

All medicines can cause side effects. According to clinical research needs, you will use Fosaprepitant, Ondansetron Sodium Chloride Injection, Dexamethasone Tablets, Olanzapine Tablets before and after chemotherapy. You can learn more about these medicines, including side effects, from their leaflets.

Side effects of the study drug:

Common adverse reactions in patients treated with fosaprepitant include hiccups, constipation, decreased appetite, dizziness, fatigue, abdominal distension, dizziness, and injection site adverse reactions. Site erythema, pruritus, pain, sclerosis, and thrombophlebitis. Allergic reactions, some serious or even fatal, are always possible when taking medicines. There are other rare side effects that your doctor will explain and discuss with you. You will need to tell the study doctor about any side effects that affect you. You will be promptly informed by the study doctor of important new information that may affect your decision to continue participating in the study.

Ondansetron Hydrochloride Sodium Chloride Injection is mainly used for the treatment of nausea and vomiting caused by drug chemotherapy and radiation therapy. Detailed information about the medicine can be found in the medicine leaflet. The adverse reactions may include headache, warm feeling in the head and upper abdomen, abdominal discomfort, constipation, dry mouth, rash, local reactions at the injection site, occasional bronchial asthma or allergic reactions, temporary asymptomatic elevation of aminotransferase. The above reactions are generally mild and no special treatment is required. Occasionally, ataxia, seizures, chest pain,

arrhythmia, hypotension, bradycardia and other rare reports have been reported.

Dexamethasone: Contact your study doctor right away if you experience any of the following serious side effects: vision problems; swelling, rapid weight gain, feeling short of breath; severe depression, unusual thoughts or behavior, seizures (convulsions); Bloody or tarry stools, coughing up blood; pancreatitis (severe pain in upper abdomen radiating to back, nausea and vomiting, rapid heart rate); low potassium (confusion, uneven heart rate, extreme thirst, increased urination, leg discomfort , muscle weakness or lameness); or dangerously high blood pressure (severe headache, blurred vision, ringing in the ears, anxiety, confusion, chest pain, shortness of breath, uneven heartbeat, seizures). Less severe side effects may include: sleep problems, mood changes; acne, dry, thin, bruised or discolored skin; slow wound healing; increased sweating; headache, dizziness, spinning sensation; nausea, stomach pain, gas; muscle weakness; or changes in body shape or body fat (especially fat in the arms, legs, face, neck, breasts, and waist).

Olanzapine is an atypical drug currently used to treat schizophrenia, and it is also clinically used to treat nausea and vomiting caused by chemotherapy. The most common (occurring in ≥ 1% of patients) adverse reactions of olanzapine are somnolence, weight gain, eosinophilia, increased prolactin, cholesterol, blood glucose, and triglyceride levels, diabetes, increased appetite, dizziness, akathisia, Parkinson's disease, leukopenia, neutropenia, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevation of hepatic transaminases, rash, asthenia, fatigue, fever, arthralgia, Elevated alkaline phosphatase, high gamma-glutamine, high uric acid, high creatine phosphokinase, and edema. Detailed information about the medicine can be found in the medicine leaflet.

Patients have experienced these side effects in previous studies, but you may also experience other side effects that are unpredictable at this time. These side effects can be minor inconveniences or serious, but if any occur, your doctor responsible for you will be watching you closely.

Although treatment is effective for your disease, these side effects can still occur.

The effect of the drug will be regularly assessed and treatment will be discontinued if no efficacy is observed.

Your doctor can exclude you from the study if the treatment was harmful to you, or you did not follow treatment instructions, or found that you did not meet the trial requirements, or the study was cancelled.

You will be notified promptly if any new information about the study drug emerges during the study that may affect your decision to continue participating in the study.

If the study drug causes direct damage to your health, and is determined by a doctor or specialist to be related to the drug, the medical staff will actively give the appropriate treatment.

Potential Risks Associated with Blood Drawing

During the study, a small amount of blood will be drawn from a vein for testing so that the study doctor can check your health. The blood draw may cause pain at the puncture site, and there is a low risk of bruising or infection at the puncture site. Some people experience dizziness, nausea, or fainting when blood is drawn.

Potential risks associated with ECG testing

Skin redness or itching may occur at the ECG electrode patch site.

7、Potential benefits

Considering the antiemetic efficacy of the olanzapine-containing quadruple regimen, after participating in this clinical study, it is possible for you to obtain better remission or control than triple therapy, but it is also possible to obtain the same efficacy as triple therapy. However, because of your participation, the research on this disease and related drugs will provide valuable experience and evidence for the treatment of such patients. Because of your positive contribution, the research collaboration group expresses its sincere gratitude to you. Thanks.

8、Research fees

During the research process, the experimental group used fosaprepitant dimeglumine for injection (produced by Jiangsu Hansoh Pharmaceutical Group Co., Ltd.), olanzapine tablets (manufactured by Jiangsu Hansoh Pharmaceutical Group Co., Ltd.), and olanzapine tablets to simulate (produced by Jiangsu Hansoh Pharmaceutical Group Co., Ltd.), Dexamethasone Tablets (produced by Guangdong Nanguo Pharmaceutical Co., Ltd.), and Ondansetron Hydrochloride Sodium Chloride Injection (produced by Jiangsu Hansoh Pharmaceutical Group Co., Ltd.) Jiangsu Hansoh Pharmaceutical Group will provide free research.

Blood collection subsidy: If you participate in the baseline blood collection of the exploratory study before the first chemotherapy, we will give you a nutritional subsidy of ￥100.

9、Compensation for Research

During the research, if you have any discomfort, or new changes in your condition, or any unexpected situation, whether or not it is related to the clinical research, you should notify your doctor in time, and the doctor will make judgment and medical treatment. If adverse events, injuries or diseases related to clinical research occur during the clinical trial, we will compensate for this in accordance with the relevant provisions of Chinese laws, but adverse reactions not related to this clinical research will not be compensated.

10、Alternative treatments outside this trial

You can also get standard medical treatment and medical management without participating in this study, namely the triple regimen of aprepitant/fosaprepitant, 5-HT3RA and dexamethasone for the prevention of nausea and vomiting caused by chemotherapy. This standard treatment regimen was used in the control group of this study. The study doctor will give you detailed instructions.

11、Withdraw from this study

During the research process, according to the design of the plan, if you feel that it is not suitable for you to continue taking the drug, the doctor in charge will voluntarily explain the reason to you and suspend the drug research. Your participation in this research is completely voluntary, you have the right to choose not to participate in this research, and you have the right to withdraw at any time during the research process. Your follow-up treatment will not be affected in any way, and you can continue to receive other treatments; You will not be discriminated against or retaliated against, nor will any of your medical treatment and rights be affected.

If you are about to withdraw from the study, please inform your responsible physician promptly. For your safety, he will conduct a full inspection of you.

Once you choose to participate in this study, we hope that you will take your medicines on time and visit and check at the agreed time without special reasons. As a research subject, you have the following responsibilities and obligations: provide the truth about your medical history and current physical condition; tell the research doctor about any problems you have during this trial; not take restricted drugs, food, etc.; Tell the study doctor if you have recently participated in other studies, or are currently participating in other studies.

12、Confidential

Your privacy will be protected. All information related to your privacy collected by this research will be kept confidential in accordance with relevant regulations. All outgoing information about you or your health from a doctor's clinic/hospital will use a number without revealing your true identity. Your identity is also not recorded in any database, speech or article.

During the study or for a period of up to 15 years after the end of the study, in addition to the study physician, the sponsor or its authorized representative, members

of the ethics committee and/or personnel of the health supervision agency in the home country (such as the China Food and Drug Administration) may have direct access to your medical records as required by local regulations, and they may have access to your identifying information. This check is to ensure that the study is being conducted correctly and/or to ensure the quality of the study data. Those who see records that reveal your true identity will keep your secrets.

While every effort will be made to protect your privacy, absolute confidentiality cannot be guaranteed. And this does not limit the responsibility of researchers and others to protect your privacy.

By signing this informed consent, you consent to the collection, acquisition, use and disclosure of your information as described above.

13、Contact person and contact information

You can keep abreast of information and research progress related to this study, if you have questions about this trial, or if you experience any discomfort or injury during the study, or have questions about the rights of participants in this study , you can contact the Ethics Committee at 020-87343009.

I hereby declare that I have read the patient information for this study described above.

- I have understood the purpose of this study, the expected benefits and risks. I understand that it is the responsibility of the study physician to provide me with any additional information about the study itself and the damage caused by the study.
- I understand that I am participating in the study voluntarily and that I may refuse to participate and/or withdraw consent and stop participating in this study at any time without penalty or loss of any other benefits I may have.
- In the context of the research, I consent to the collection and processing of

research data by the investigator and sponsor, including information about my health. I agree that data from my research may be processed in confidence by site staff, sponsor's commissioned staff, and health regulators. I agree that the sponsor or its principal may have direct access to and access to my original medical records to verify the procedures and/or information of the clinical study, again in a private and confidential manner. I agree that even if I withdraw from the trial, the data collected about me can still be used.

- I hereby sign this consent form indicating that I am voluntarily participating in this study. I have come to realize that investigational therapy is an experimental treatment and carries risks.
- My name or any information that could identify me as a research participant will not be disclosed except as required by law or regulation or authorized by myself/legal representative.

I affirm that I have answered the doctor's questions about my medical history truthfully and agree to accept the study doctor's arrangements for me. After signing the consent form, I will get a copy.

Patient's name（regular script）_____ Patient's signature _____ date_____

If the patient has appointed a legal principal (if applicable):

Client's name （regular script） _____Client's signature _____ date_____

Witnesses (if applicable):

Witness' name （regular script） _____ Witness' signature _____ date_____

Investigator's name （regular script） _____Investigator's signature _____ date_____