Patient Information Sheet and Informed Consent Form

"The clinical study of the safety and efficacy of Istaroxime in Treatment of Acute Decompensated Heart Failure - A multicentre, randomized, double-blind, placebo controlled, parallel group clinical study-"

Protocol N° CVT-CV-002 (Final version, 23 July, 2015) - EUDRACT N°: 2013-000540-26

Dear Mr./Mrs.,

The heart failure is a highly disabling condition that negatively impact the quality of life. You have been hospitalized for a further worsening of your symptoms (breathing difficulty, fatigue). The drugs usually administered to a patient like you (diuretics, traditional inotropes) are only partially effective and are associated in some cases to a worsening of the patient conditions during the following weeks and months. Therefore, it will be important to can use new drugs able to improve in the future both your symptoms and your conditions. Istaroxime is a new drug with favourable characteristics for the treatment of patients with the heart failure. Its effectiveness and tolerability have been demonstrated after a short-time infusion (6 hours), but data concerning the infusion of 24 hours are lacking. This will be evaluated in this clinical study that is aimed at demonstrating the security, tolerability and efficacy of Istaroxime 24 hour infusion in comparison with placebo in patients with heart failure.

With this document, you have been asked to participate in the above mentioned Research.

This document is aimed at informing you about the purpose of the study. You are asked to carefully read this written document of informed consent and ask all your questions to the Physician who is responsible of this Research, and to the Physician who will follow you during the study in order to take a conscious decision on your participation. You are not obliged to participate to this study, and if you decide to not participate, this decision will not impact on your future medical assistance. If by reading this document, you will have any questions, you can ask at any time explanations about the terms or information that are not clear to you. In case whereby, after having read and understood all the information provided, you decide to take part in this clinical trial, you will be asked to personally sign and date the Informed Consent Form attached to this document and one copy will be delivered to you for keeping it. Before taking any decision, if you want, you can ask an opinion to your relatives or to your Physician.

1. Basic Information

a. Which is the purpose of this clinical study?

The heart failure is a clinical condition that does not permit to the heart to pump blood in order to cope with the body need. It is a widespread pathology that affects more than 30 million of people worldwide. During acute heart failure episodes, the ability of the heart to pump blood from the pulmonary circle to the peripheral circulation is impaired and, among the various symptoms, the most serious ones are the difficulty to breathing and a serious fatigue. You have been hospitalized for a worsening of your symptoms. The therapy you are following has not avoided a worsening of your symptoms. In this case, it is necessary an intravenous therapy. The drugs that at the moment are used for the intravenous therapy are only partially effective and, in patients with low systolic blood pressure or at the lower normal limits, as you, can favour the development of other cardiac complications (coronary insufficiency, arrhythmias, long-term myocardial damage).

Istaroxime is a drug developed for increasing the cardiac ability to pump blood in this kind of patients without inducing the above mentioned complications. Istaroxime is an experimental product, that means that its use has not been yet approved by a special monitoring Agency like the Food and Drug Administration (FDA) from USA and the European Medicinal Agency (EMA).

The aim of this clinical trial is to confirm the safety and efficacy of an intravenous (iv) infusion of Istaroxime for the treatment of the acute heart failure. Other objectives of this study are the evaluation of the Istaroxime and its by-product blood levels after its administration.

b. Who is sponsoring this clinical study?

This clinical study is financed by the **CVie Therapeutics Company Limited** and by **Dr. JUN Huang**, who represents the Study Sponsor, thus meaning that they are responsible for the starting, managing and /or financing of this clinical study.

c. Why have you asked me to participate to this study?

You have been asked to this study because you have been hospitalized for the treatment of the acute heart failure and because the Study Physician have considered that you could have benefit from this drug. The inclusion criteria to the study include a physical examination and laboratory analysis that will be evaluated before you can be enrolled in this study. The decision to participate to this study is exclusively yours. If you decide to not participate this will not negatively impact on your medical care.

d. How many other subjects like me will participate to this study?

About 120 subjects will participate to this study, among which 24 cases coming from Italy, 96 cases from China.

e. Which kind of experimental product/s will be investigated in his study?

The only experimental product that will be investigated in this study is Istaroxime, administered at two different doses 0.5 and 1.0 μg/kg/min and compared with placebo. Placebo is an inactive drug that resembles from outside to the true drug, but does not contain any active drug; it is therefore completely inactive and not dangerous. In this document istaroxime is defined as "experimental product". The experimental product will be administered to you by intravenous route (i.v.) for 24 hours.

f. Which probability I have to receive the experimental product?

If you meet the enrolment criteria and you decide to participate to the study, you will be assigned at random (as for tossing a coin) to one of the two treatment groups (istaroxime or placebo). Istaroxime will be administered a low or high dose. If you will be assigned to receive istaroxime and you will be included within the first 60 subjects enrolled in the study, you will receive the low dose; if you will be within the second group of 60 subjects enrolled in the study you will receive istaroxime at high dose. The assignment to istaroxime or placebo is based on a list created by a computer. The probability to receive istaroxime will be of the 66.6% (2 over 1).

g. Can I know which product (istaroxime or placebo) I'm receiving?

Since this is a blind study, neither you nor your Study Physician or the study personnel will know the group you belong (istaroxime or placebo). The reason of this is to be sure to be not influenced when judging the safety and efficacy of the experimental product. If needed, in emergency situation, the information on the treatment will be available.

h. How long does the study last?

The length of your participation to this study will last about 1 month (30 days). A Screening period, not longer than approximately 24 hours, the i.v. infusion for 24 hours, daily evaluations during your hospitalization up and not after day 4, and finally, one final medical evaluation at day 30 are planned. Your Study Physician or the Sponsor can decide to exclude you from the study at any time.

2. Study Procedures

a. Which are my responsibilities if I participate to the study?

If you participate to this clinical study, you will be asked to sign this form of informed consent. To establish your eligibility to the study, you will be subjected to a series of screening procedures (see below) including questions about your cardiac failure and the therapy received for your pathology, and questions concerning other clinical conditions affecting you. The screening procedures will be performed within 24 hours from the signature of this form of informed consent for the treatment of your cardiac failure.

If you will be eligible to this study and accepts to participate, you will receive the experimental product or placebo by iv infusion for 24 hours as global. Due toyour clinical conditions, your hospitalization will last al least 4 days, which corresponds to the minimum hospitalization time for the acute heart failure. The final evaluations are planned about 1 month after your enrollment in to the study and you will be asked to come back to our Centre for a medical visit.

b. Which kind of analysis or procedures is expected in this study?

Screening phase

After signing the informed consent form, you will be subjected to a screening to establish if you are eligible for this study. The following evaluations and procedures will be performed:

1. Evaluation of all the inclusion or exclusion criteria of the study;
2. Evaluation of your medical and pharmacological assessment, collection of your demographic data;
3. Physical inspection
4. ECG;
5. Holter ECG;
6. Blood and urine sampling for laboratory analysis;
7. Pregnancy test (only for child-bearing women);
8. Echocardiography;
9. Recording of any medical event that can happen during the screening phase

Treatment and follow-up:

After having concluded the screening phase and you will be considered elegible for the enrolment, the i.v. treatment with the experimental product will start. The day of starting of the treatment is defined as day 1 of the study. The i.v. infusion of the experimental product will be performed within 24 hours. During this period and for further 48 hours after the experimental drug administration, you must be hospitalized (up to day 4 of the study). Beside the procedures listed below, during all the time of your participation to the study, the Study Physician or the Study personnel will record the other medical treatments you will receive and any medical or hospitalized event that you could receive.

Day 1 of the study

After starting the experimental product administration, the following evaluations will be performed:

1. Blood sampling for laboratory analysis;
2. Vital signs;

3. ECG;
4. Holter ECG;
5. Echocardiogram;
6. Recording of any medical event

Day 2 of the study:

1. Physical examination;
2. ECG;
3. Holter ECG (only if needed);
4. End of the experimental product infusion;
5. Echocardiogram;
6. Blood sampling for laboratory analysis;
7. Recording of any medical event

Day 3 of the study:

1. Physical examination;
2. ECG;
3. Blood sampling for laboratory analysis;
4. Recording of any medical event
5. Echocardiogram;

Day 4 of the study:

1. Physical examination;
2. ECG;
3. Blood sampling for laboratory analysis;
4. Recording of any medical event

Day 30 of the study:

The final evaluations will be performed about 1 month after the start of your participation into the study. Unless you is not yet hospitalized, you will be asked to come back to the experimental Centre. The following procedures and evaluations will be performed:

1. Physical examination;
2. ECG;
3. Blood sampling for laboratory analysis;
4. Pregnancy test only for child-bearing women;
5. Recording of any medical event

Further information on the study procedures

During the study, due to the need of related laboratory examinations, the global volume of collected blood will be about 165 ml, which means about one third of a typical blood donation (500 ml). The blood sample will be collected within 4 days. During all the study period, all your side effects will be monitored. If a relevant side effect or abnormal laboratory data will happen, you could be asked to have further medical visits at the experimental Centre up to when the situation is solved or is considered stable by the Study Physician.

c. What does it happen at the end of the clinical study?

It is planned that your involvement in the study will end about 1 month after the starting of the i.v. infusion of the experimental product. However, since you are a volunteer participation, you can leave the study when you desire. If after the end of the study you think to have had a side effect related to the experimental product or to the study procedures, you must contact your Study Physician: Dr._____ by the telephone number:_____.

3. Safety: POTENTIAL RISKS AND DISCOMFORTS

a. Which are the general risks of participating to this research study?

168 adult subjects have been treated with different doses of istaroxime in clinical experimentations, without showing evidence of severe dangers for the heath and the welfare of the patients. However, the administration of any experimental product requires a careful evaluation of possible side effects. Since istaroxime is an experimental product, not all the potential side effects in human being are known. The side effects are medical unfavorable conditions or consist in a worsening of a pre-existing medical condition and they can happen during the participation to a study or, generally speaking, when undergoing to a therapy. One of the aims of this study is to know the possible side effects of istaroxime. The Study Physician will keep you under strict observation during the study and will discuss with you about any possible problems related to the risks, discomforts and side effects, If you participate to the study, during the study you or one of your relatives must immediately warn the nurses or the Study Physician in case of unusual health condition, lesions or side effects. If you have any concern about the study, contact your Study Physician.

b. Which are the known side effects of the experimental product?

No serious adverse events (such as death or serious cardiovascular events) have been happened during the previous 3 studies on patients with acute heart failure. The only observed side effects were: gastroenteric discomforts, emesis or diarrhea, and pain at the drug injection site at doses higher than those tested in this study. At the doses used in this study, this kind of side effects was observed in 2 patients over 60.

As for any other drug, you can have an allergic reaction to Istaroxime. The possible symptoms include headache, skin rushes, flushing, swelling, breath shortness, nausea and sometime vomits. The allergic reactions can be also serious or endangering of life, such as dizziness, difficulties in breathing or swallowing or a reduction of blood pressure. If you should experience any of these symptoms during the study, you must immediately warn you Study Physician.

c. Which are the risks associated to the experimental product in association with other drugs?

The risks due to the use of istaroxime in association with other drugs are not known. At screening, you must inform the Study Physician about all the drugs you are taking and, during the study, you must inform the Study Physician before taking any other new drug and before changing the drugs you are currently taking.

d. Which are the risks associated to the procedures of this research study?

Your Study Physician will discuss with you the possible risks associated to the analysis and procedures planned for this study (for instance, blood sampling, diagnostic imaging, echocardiogram, intravenous administration or other medical procedures).

Blood sampling

During the study, blood will be periodically taken. The possible side effects of blood sampling are soreness, pain, bleeding, bruising and /or infection at the injection site. Blood sampling may cause nausea and/or dizziness.

Electrocardiogram (ECG)

ECG is an examination that measures the electric activity of the cardiac beating by using electrodes (small adhesive disposable disks put on the skin). Neither pain nor risks are associated to the ECG. When the electrodes will be removed, you could feel a light discomfort or skin irritation.

Continuous intravenous administration

The experimental product will be administered by continuous intravenous infusion for 24 hours through a venous catheter inserted in a high blood flow vein. The rare complications

are associated to this procedure are: vessel lesion, of the catheter, phlebitis, infections.

e. What does it happen if I /my partner became pregnant during the study?

Since this is an intravenous administration lasting 24 hours, performed in the hospital and followed by 3-4 days of hospitalization, this case is highly improbable.

However, if you are a woman and became pregnant or suspect to be pregnant during this study, you must immediately inform the Study Physician. The treatment with the experimental product will be immediately stopped and your safety (related to the pregnancy) will be monitored up to the study conclusion. Your Study Physician will ask you your consent for furnishing to the Sponsor of the study information about the pregnancy and the child.

If you are a man and your partner is or became pregnant during the study, you must immediately inform the Study Physician. Your Study Physician will ask you contact information and your consent for furnishing to the Sponsor of the study information about the pregnancy of the mother and the child. The men of the study whose partners are or became pregnant should practice abstinence or use the condoms for at least 5 days from the end of the treatment with the experimental product to guarantee that the unborn baby cannot be exposed to istaroxime through the seminal fluid.

4. POTENTIAL BENEFITS

a. Which are the therapeutic benefits foreseen for this experimental product?

Istaroxime is currently under development for the treatment of the cardiac failure. The potential benefits, listed above have been demonstrated after 6 hour infusion. However, it is not known if these benefits are also present after 24 hours of infusion. This study has been planned to ask this question.

b. Will I get benefit by participating to this study? Will other subjects get benefit?

For the reasons listed at paragraph n°1, you could get a direct benefit by participating to this study due to the favorable effects of the drug in patients with low or at the lower normal limits of arterial blood pressure. Of course, you will not get this benefit if you will take the placebo. Other subjects, in the future, could get benefits from the knowledge about this study. This information could allow the Physicians to better know the experimental product use for the acute heart failure in patients like you for whom the present therapy is not satisfactory.

5. ALTERNATIVE THERAPY

a. If I decide not participating to this study, are there other alternative available treatments or drugs to this treatment?

Your alternative at the treatment with this experimental product, it is not to participate to this study. You should discuss with your Study Physician to know other treatment options that may be available for you. These options can include an increase of the dose of the drug you are currently taking for curing your cardiac failure or adding new treatment.

b. Are there any benefits with these new treatments? Are there any risks?

All type of treatments deserves benefits and potential risks. Your Study Physician can explain you all the treatments available for you and their benefits and risks.

6. POTENTIAL COSTS/REMBOURSES

a. How much does this study cost to me?

The sponsor of this study will provide experimental product and related examinations for free.

b. Can I be reimbursed for any expense I can have as consequence of the study?

To participate to the Study you will not receive any compensation. If you have a private health insurance it is better if you verify with your insurer that your participation in the study does not impact on your insurance, before consent to participate.

c. Will I receive any compensation for the use of my biological sample?

You should know that, by the use of your samples in the Study, a commercial pharmaceutical product and/or a procedure could be developed. The Sponsor, other researchers or research company can patent or sell discoveries produced by this research. If this happens, neither the Sponsor nor the Study Physician will give you any compensation.

7. CONFIDENTIALITY

a. a. How the confidentiality of my clinical documents will be protected?

The management of the medical information obtained by the clinical research is governed by national and international rules on the data protection and medical confidentiality (Good Clinical Practice (GCP)). The medical information collected during this study will be firstly verified for their accurateness. Then, it will be transferred in the study data bank and processed for analyzing, disclosing and publishing the study results for scientific aims

The confidentiality of your clinical documents will be protected according to the currently regulations. If the results of the experiments will be published, your identity will be kept

confidential. The results and other information of the study could be transmitted to the Regulatory Agencies of the Countries where the experimental product is under evaluation for the approval. Neither your results nor your samples will be identified by your name. The data related to your participation in the study will be associated to you by a number that identifies the person, the birth date and the sex.

b. Who will have access to my medical information if I sign this Informed Consent Form?

Your participation to the study must be annotated in your clinical folders. If the Physician who will follow you in this study is not your family doctor, the latter shall be informed of your participation to the study. The representatives of the Sponsor can ask to have a direct access to your clinical documents to verify the information collected for the study. Your clinical folders can also be examined and photocopied by the members of the Ethical Committee of the experimental Centre, of a Regulatory Agency or by an authorized Sponsor representative. This people can know your name, other personal information such as the birth date and the sex, your medical information, but they do not disclose your name to others. By signing this Informed Consent Form, you (or your legal representative) authorize the access to these confidential information. The paragraph "information of the personal data management", at this Informed Consent Form, will give you further information on the management of your personal data related to the study. Some of your data, including the ECG, that can contain confidential information, can be send to a central office for the analysis and interpretation and then send to the Sponsor and/or the Study Physician. The members of the personnel of the central office will keep the confidentiality of your information.

8. DAMAGES

a. What can I do if I presume to have suffered a damage as consequence to the participation at this study?

If you think to have suffered a damage that are connected to the study, you must alert your Study Physician. The Study Physician and the study personnel will give you the needed treatment.

b. If I will suffer a damage because of the participation to the study will I be reimbursed?

In case of any damage caused directly to your participation to the study you will be covered by a special insurance entered into by the Sponsor with the Insurance Company. Insurance companies will be based on relevant laws and regulations and insurance policy, your insurance compensation accordingly.

9. INFORMATION ON THE PROCESSING OF THE PERSONAL DATA

a. Use of the data and related objectives

The Centre and the Sponsor of the study, each one according to their competence and responsibility as required by the Good Clinical Practice will utilize, analyze and manage your personal data, with particular reference to your health and other data related to your origin, your life style etc., only for the conductance of the study as indicated below and for pharmacovigilance purposes, with the final objective to develop commercial pharmaceutical products. To this end the data will be collected by the Study Physician and his/her collaborators and, after their coding, they will be transmitted to the Sponsor and to the people and external Societies working by their self or making assistance to the clinical experiments or who will know the data as responsible of the data management. Some of these external Societies can be located also in foreign Countries outside Italy and China. The whole list of the external societies will be stored at the Experimental Centre. Your personal data, including information of your health condition, will be collected, used and managed by the above cited societies and will be analyzed by the Sponsor and his delegates to discover whether Istaroxime is beneficial for subjects suffering of acute cardiac failure. This is indispensable for the study development: if you If you have suffered a damage/developed a disease related to the study, the Study refuse to furnish your personal data, you could not participate into the study.

b. Data Characteristics

The Physician who will follow you during the study will identify you by a personal code number (code): your data collected during the study, except your name, will be transmitted to the Sponsor or his designated persons, and will be recorded, analyzed, used, managed and stored with your code, your birth date, sex, weight and height. Only the Study Physician and the authorized persons can link this code to your name.

c. Management of the data

Neither the results nor your samples (if collected) will be identified with your name. If the results of the clinical study will be published your identity will be kept anonymous. Your participation into the study implies that, according to the laws on the clinical experimentations of drugs, the Sponsor personnel or the external societies that monitor and verify the study on behalf of the Sponsor, the Ethical Committee and the health authorities can have access to your data, including those contained in your original clinical folder, in a manner such as to ensure the confidentiality of your identity.

d. Exercise of the Rights

You can exert the Rights on the Confidentiality of your data according to law that controls such matter.

However, you cannot know which drug you will receive and/or the results obtained during the development of the study. You can stop at any moment and without give any explanation your participation into the study: in this case, your biological sample (if collected), when no more needed for the study, will be destroyed and no other data on your person will be collected. However, the data already collected will be used and disclosed according to this form.

You should inform your family Doctor or other Physicians of your participation into the clinical study. Furthermore, you must authorize the Study Physician to contact other Physicians who take care of you. If you want, the Study Physician can inform you about the general results of the study and, in case, of data useful for your disease, if produced.

10. Rights and Obligations

If I will accept to participate into this study, which warranties can I have?

You are a a voluntary participation and you are free to withdraw from the clinical study at any time without problem for your future medical care. If you decide to withdraw, you must warn the Study Physician in order to interrupt your participation in a correct way and discuss your future medical care. Furthermore, your Study Physicians or the Sponsor can decide towithdraw you from this clinical study.

- You, or your legal representative will be immediately updated about any information on your will to continue to participate into the study. According to your Study

Physician and the Sponsor, it is possible that you or your legal representative can be asked to sign a revision or an appendix of the Informed Consent Form giving this information.

- You can ask about this study at any time. If you think to have suffered from an adverse side effect to the experimental product or to the procedures, or you feel always bad during the study, you must contact your Study Physicians.

If you have any questions about the Informed Consent procedure or your rights as subject involved into the clinical study, you can contact your Study Physicians.

If you want to file a complaint or consult questions concerning your rights as a study participant, please contact the Ethics Committee of Jiangsu Province Hospital by 025-68136360 (phone number).

11. SIGNATURES

By signing this Form, I undersigned (add name and surname) ……..

- I confirm that I have had adequate opportunity to discuss all the available treatments and all my doubts and my questions on this study have been satisfactory clarified.
- I agree that the research carried out by the Sponsor of the study, by using my clinical data collected during this study, could lead to the development of commercial pharmaceutical products. The Sponsor and other researchers could use these data to patent and sell the discoveries coming from the results of this research. In this case, neither the Sponsor nor other participants to this research will give me any reward.
- I agree that my personal data can be confidentially treated and can be transferred out of China, to subjects or societies indicated in the Information at paragraph 9 of this document and in particular to the Sponsor for the research objectives within the limits and the mode indicated in the present Information form. I undertake to inform my family doctor and any other physicians who will cure me about my participation in this study.
- I authorize the Study Physician to directly contact any other physicians who will cure me.
- I undertake to avoid to became pregnant (to make pregnant) up to 5 days after the study product administration.

By signing this Form, I confirm to agree to participate to this study and to have receive a copy of this Informed Consent Form.

_____ _____

Subject signature date *

Contact information: _____ ID No.: _____

OR

_____ _____

Legal Representative signature date

(The document must be signed by legal representative when the subject age more than 65 years old.)

Contact information: _____ ID No.: _____

Relationship with the subject

- * Who is signing must write by him/herself the date.

I undersigned (add name and surname)……
as Study Physician, confirm to have furnished to the subject comprehensive explanations about the nature, the aim, the length and the potential risks associated to this study, and I believe in conscience that they have been understood.

_____ _____

Study Physician signature date *

Contact information: _____

* Who is signing must write by him/herself the date.