PATIENT INFORMATION SHEET

“A randomised open-label, multicentre, parallel-group, non-inferiority trial FORPE of Fortelyzin® («SuperGene», LLC) single bolus administration and Actilyse® (Boehringer Ingelheim Pharma GmbH) bolus-infusion administration in patients with massive pulmonary embolism”

Version 1.0 of September 01, 2018
Sponsor: «SuperGene», LLC, Russia

Clinical site: _____

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Dear petient!

You have been invited to participate in a clinical trial of the medicinal product Fortelyzin®. Before you agree to participate in the trial, it is important that you understand what it involves. Read this information carefully. Assess the risks and benefits that you may receive from participating in the trial. Ask the physician to explain any unclear words or proposed actions. You will be given full answers to any questions you may have regarding participation in the trial in an accessible form. Once you decide to participate in the trial, you (or your legal representative) must date and sign this document and receive a signed, dated copy.

The patient signs two copies of the Informed Consent Form. One copy of the signed and dated written Informed Consent will be given to the patient, the second will be kept by the investigator.

A prerequisite for conducting a clinical trial is your (or your legal representative's) written consent to participate in it. Please read the text below carefully in addition to the interview with your doctor, and ask questions if you do not understand anything.

Please provide your written consent to participate in a clinical trial only if:

- You fully understand the method and course of the clinical trial;
- You are willing to participate in this clinical trial;
- You are aware of your rights as a participant in this clinical trial.

After signing the Informed Consent form for participation in the trial, each patient will be assigned an unique patient identifier (UPI) in accordance with applicable law. The UPI is established by the insurer based on the data of the patient participating in the clinical trial provided by the researcher.

The aim of this trial is to evaluate the efficacy and safety of a single bolus administration of 15 mg of Fortelyzin® in patients with massive pulmonary embolism (PE). The rights, safety and well-being of the trial participants will be a priority and prevail over the interests of science and society.

Information about the drug

Fortelyzin® is a new thrombolytic drug developed by «SuperGene» LLC. The active ingredient of this drug is the substance Forteplase®, which is a recombinant protein containing the amino acid sequence of non-immunogenic staphylokinase. Staphylokinase is an active substance capable of dissolving intravascular thrombi that cause acute myocardial infarction. The difference between Fortelyzin® and staphylokinase is that Fortelyzin® is not neutralized with repeated administration. Efficacy of staphylokinase-based drugs in patients with acute myocardial infarction has been confirmed by a number of foreign clinical studies, as well as Fortelyzin® clinical trials conducted in leading cardiology clinics in Russia. Based on clinical trials results, Fortelyzin® was registered as for medical use: registration certificate LP-001941 dated of December, 18, 2012. Since 2015, Fortelyzin® has been included in the list of vital and essential medicinal products (Government Order No. 2782-r dated of December, 30, 2014).

Fortelyzin® is a lyophilisate for the preparation of a solution for intravenous administration, 5 mg (745,000 IU).

Composition per 1 vial:

Active ingredient: Forteplase® (recombinant protein containing the amino acid sequence of staphylokinase) 5 mg (745,000 IU).

Excipients: L-arginine 15.0 mg, L-histidine 2.0 mg, glycine 30.0 mg, povidone-17 20.0 mg, polysorbate-20 0.4 mg.

Solvent: Sodium chloride injection solution 0.9%, 5 ml - 1 ampoule.

Comparator drug: Actilyse® (INN - alteplase).

Manufacturer: Boehrninger Ingelheim Pharma (Austria)

Dosage form: lyophilisate for the preparation of an infusion solution complete with a solvent.

Lyophilisate: white or pale yellow mass; solvent: Colorless transparent liquid

Active ingredients: alteplase 1 vial 50 mg (taking into account the excess of 51.5 mg);

Excipients (taking into account the excess): L-arginine 1742.0 mg (1790.8 mg), phosphoric acid 536.0 mg (551.0 mg), polysorbate 80: 3.5-5.0 mg (≤ 5.1 mg).

Residual traces: gentamicin (used in the manufacturing process).

Solvent: water for injection 50 ml - 1 vial.

1 ml of solution after dilution contains 1 mg of alteplase.

The trial was approved by the Ministry of Health of the Russian Federation, and the Ethics Council of the Ministry of Health of the Russian Federation.

The sponsor of the trial is «SuperGene», LLC.

This trial will involve 310 patients with massive PE. The duration of your participation in the trial will be 30 days.

How the trial will be conducted?

This trial will be conducted in full compliance with the ethical principles set out in the Declaration of Helsinki of the World Medical Association “ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1964-2008)”, Federal Laws No. 323 “On the Fundamentals of Health Protection of Citizens in the Russian Federation”, No. 61 "On the Circulation of Medicines", the National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice", ICH harmonized tripartite guideline: Guideline for Good Clinical Practice.

During the trial, six visits will be planned, five of them will be conducted during the hospitalisation, and the 6th visit will be conducted on an outpatient basis on the 30th day. You give your consent to use contraceptive methods throughout the trial period and for 3 weeks after its completion.

Visit 1. (Start of the trial)

Prior to administration of the trial drug, all patients will undergo the following procedures:

- determination of inclusion/exclusion criteria
- signing of informed consent form
- collection of demographic data (date of birth, gender, body weight)
- collection of medical history (duration of the underlying disease, previous therapy, allergological anamnesis, etc.)
- physical examination
- PESI risk stratification
- Computed tomography with contrast of the pulmonary artery (CTPA)
- Echocardiograpy (EchoCG)
- ultrasound diagnostics of the inferior vena cava
- determining of the haemodynamic collapse
- Electrocardiography (ECG)
- blood sampling for hematological and biochemical analyses
- coagulogram
- general urine analysis
- randomization
- Fortelyzin® or Actilyse® administration

Visit 2. (Day 1 after thrombolysis)

- assessment of vital signs – every hour
- determining of the haemodynamic collapse
- changes in organs and systems
- CTPA
- EchoCG
- Ultrasound diagnostics of the inferior vena cava
- ECG
- general blood test
- coagulogram

- general urine test
- registration of adverse events (AEs)
- assessment of bleedings
- concomitant therapy changes

Visit 3. (Day 2 after thrombolysis)

- assessment of vital signs (twice per day)
- determining of the haemodynamic collapse
- changes in organs and systems
- registration of AEs
- assessment of bleedings
- concomitant therapy changes

Visit 4. (Day 7 after thrombolysis)

- assessment of vital signs (twice per day)
- determining of the haemodynamic collapse
- changes in organs and systems
- EchoCG
- ultrasound diagnostics of the inferior vena cava
- ECG
- general blood test
- registration of AEs
- assessment of bleedings
- concomitant therapy changes

Visit 5. (Discharge)

- assessment of vital signs
- changes in organs and systems
- EchoCG
- ECG
- general blood test
- general urine analysis
- registration of AEs
- assessment of bleedings
- concomitant therapy changes

Visit 6. (Day 30 after thrombolysis)

- assessment of vital signs
- registration of AEs
- assessment of bleedings
- concomitant therapy changes

Unscheduled visits

Unscheduled visits may be conducted at the discretion of the Investigator or at the initiative of the patient. For all unscheduled visits, the corresponding case report form (CRF) page should be filled out.

Physical examination will be performed by the investigator. It includes assessment of the patient's general condition and the following body systems: lymph nodes, mouth, and pharynx, lungs, cardiovascular system, abdominal cavity, extremities, musculoskeletal system, nervous system, and skin.

All changes considered clinically significant will be reported as an anamnesis before the trial drug administration, and after the patient received the trial drug, all changes will be reported as adverse events.

Vital signs include blood pressure, heart rate, and respiratory rate, which must be measured and recorded by the staff of the research center. Measurements of blood pressure and heart rate will be taken at the same body position throughout the trial.

Electrocardiography (ECG) will be performed in accordance with normal clinical practice. A prerequisite is the registration of all 12 standard leads. ECG interpretation is performed by an authorized researcher.

Computed tomography with contrast of the pulmonary artery (CTPA)

CTPA is the most common method for PE diagnosing (level of evidence 1A). It has wide capabilities for visualizing the lumen of the pulmonary arteries, the nature of the vascular bed lesion, identifying pulmonary infarctions, and, when simultaneously performing a native study of the lungs, conducting a differential diagnosis.

PE is diagnosed when thrombi are detected in the segmental (distal) and more proximal branches of the pulmonary arteries.

Currently, CTPA is the standard for non-invasive PE diagnostics due to its high sensitivity and specificity. Single-detector CTPA has a sensitivity of 70% and a specificity of 90%, and multidetector CRPA has a sensitivity of 83% and a specificity of 96%.

Echocardiograpy (EchoCG)

EchoCG is an informative and accessible non-invasive method for examining PE patients. According to EchoCG, PE presence can be predicted or denied with high accuracy. EchoCG examination has many fairly specific symptoms for PE diagnostics. PE is supported by: enlargement of the right chambers of the heart, bulging of the interventricular septum towards the left parts, paradoxical movement of the interventricular septum in diastole, direct location of the thrombus in the pulmonary artery, severe regurgitation on the tricuspid valve, 60/60 sign, McConnell sign. Positive echocardiography results may be the basis for PE diagnosis. The criterion for right ventricular dysfunction (RVD) is an increase in pulmonary artery systolic pressure (PASP) of more than 30 mm Hg in combination with RV enlargement more than 30 mm. The following parameters are also assessed: right atrium diameter, RV/LV end-diastolic (EDD) ratio, RV free wall hypokinesis, thrombosis of the right chambers heart, paradoxical movement and/or flattening of the interventricular septum.

Utrasound diagnostics of the inferior vena cava

The trial is carried out to identify PE source (thrombosis) and the likelihood of recurrent PE (the presence of floating blood clots). The deep veins of the leg, popliteal veins, superficial femoral veins, common and deep femoral veins, external and common iliac veins, the inferior vena cava, as well as the great and small saphenous veins are examined on both limbs. If there is no thrombosis in these veins, it is necessary to examine the internal iliac, gonadal (testicular), renal and hepatic veins. A reliable sign of thrombosis should be considered the absence of closure of the vein walls during compression by a sensor installed across the vein.

General and biochemical blood tests

These tests will be carried out in accordance with the methodology adopted in the clinical site laboratory. The following parameters will be measured:

– general blood test (number of red blood cells, white blood cells, platelets, haemoglobin, haematocrit, leukocyte formula, ESR)

– biochemical blood tests (glucose, NT-proBNP, ALT, AST, bilirubin, creatinine, total protein, sodium, potassium, CK, urea, cholesterol, HDL-C, triglycerides)

– coagulogram (fibrinogen, INR, APTT, prothrombin, D-dimer).

If you will be included in the trial based on the examination, you will be administered the trial drug Fortelyzin® at a dose of 15 mg or Actilyse® in accordance with the instructions for use. The choice of Fortelyzin® or Actilyse® will be made randomly using the "envelope" method. This assignment procedure is called randomsation. This method gives all patients an equal chance of receiving Fortelyzin® or Actilyse®.

You will be under constant medical supervision in the future.

All adverse events will be closely monitored during the trial. If they occur, all available data will be assessed and appropriate measures will be taken by the research center staff.

Throughout the trial, in addition to Fortelyzin® or Actilyse®, you will receive treatment in accordance with current Guidelines (Russian Clinical Guidelines for the Diagnosis, Treatment, and Prevention of Venous Thromboembolic Complications and Standards of Medical Care for Patients with Massive PE) adopted in the medical institution where you are hospitalized.

After thrombolysis, anticoagulant therapy with unfractionated heparin will be started for 24 hours.

In patients with massive PE, massive infusion therapy is not recommended, since aggressive volume loading can worsen right ventricular dysfunction.

There are no alternatives to thrombolysis for the treatment of massive PE.

Risks and Benefits of Participating in the trial

Your physician will make every effort to minimize any discomfort that may be associated with the trial procedures.

Massive PE is one of the most common cardiovascular diseases. The pathology is expressed in the blockage of one of the pulmonary arteries or their branches by blood clots (thrombi), often formed in large veins of the legs or pelvis. PE is the blockage of the lumen of the pulmonary artery by a floating (moving) thrombus.

Treatment is aimed at eliminating the thrombus blocking the lumen of the vessel. Thrombolytic therapy is used for this purpose - this is the breakdown of thrombi with the help of drugs.

The expected benefit from using the drug is the restoration of normal blood circulation in the pulmonary artery, which will normalize the contractile function of the heart, avoid the development of heart failure and death in patients.

Possible adverse effects of Fortelyzin® include the likelihood of bleeding. Minor bleeding (injection sites, oral cavity), as a rule, does not require additional treatment.

Internal bleeding may occur, which may be caused by a latent form of peptic ulcer disease, esophageal erosion, bleeding from haemorrhoidal veins, esophageal veins, etc. In this regard, careful collection of anamnesis with a wary attitude to the presence of the above diseases and a clear selection of patients taking into account contraindications allow, in most cases, to reduce the risk of bleeding to a minimum level.

In patients with massive PE, intracranial haemorrhage may develop during thrombolytic therapy. However, it is believed that the benefits of using drugs of this group in patients with thrombosis significantly outweigh the risk of bleeding. During the trial, all adverse events will be carefully monitored. If they occur, all available data will be assessed, and the research center staff will take appropriate measures.

Fortelyzin® has undergone clinical trials in the leading clinics and has shown clinical efficacy in patients with myocardial infarction comparable to that of Actilyse®.

To minimize the risk, you should inform your doctor about all your existing diseases and conditions that may be accompanied by bleeding (haemorrhoids, gastric ulcer and duodenal ulcer, fibroids, recent surgery, etc.).

Allergic reactions are rare when using thrombolytic drugs. There is virtually no risk associated with the tests and examinations (general and biochemical blood tests, coagulogram, general urine test, blood pressure measurement using a mercury manometer or aneroid manometer, resting ECG in 12 standard leads, echocardiography, CTPA), which are required by the conditions of this trial. During the trial, you will be under constant medical supervision. You must immediately report any changes in your health to the medical staff. If any adverse events occur, they will be assessed, and you will be provided with qualified medical care in full.

Participation in the trial and compensation

There is no payment for participation in the trial. All laboratory tests, instrumental examinations and medical consultations related to the trial are free of charge. The trial drug Fortelyzin® and Actilyse® are also provided for free.

No other compensation methods (such as for loss of time, wages, moral damages) are provided.

By signing this Informed Consent Form, you become a participant in a clinical trial. However, you do not lose any rights that belong to you by law.

Participation in a clinical trial may be a violation of the terms of the voluntary health insurance contract.

Insurance

The health of patients participating in this clinical trial is insured. If your health will be damaged during the trial and this damage will be a direct consequence of the action of the trial drug, the Insurance Company will cover the costs to ensure an adequate volume of medical care.

For trial period, you will be insured in "ALLIANCE" LLC in case of harm to your health. Insurance is provided for in a separate contract. The insurance policy will be issued to you after signing the Informed Consent Form. In the event of damage to your health, the connection of which is proven with the intake of the trial drug, and provided that you strictly followed all the requirements of the trial Protocol and the recommendations of your attending physician, "ALLIANCE" LLC will pay compensation for the provision of necessary medical care, the purchase of drugs and other expenses related to the deterioration of health.

Contact numbers of "ALLIANCE" Insurance Company: 8 (495) 232-32-32.

Patient responsibility

During the trial, you can take other drugs to treat any concomitant diseases you have. Their intake must be agreed upon with the trial physician (excluding the need for emergency medical care). You must provide the physician with detailed medical information about yourself, strictly follow all trial procedures and physician's recommendations, and also immediately inform the medical staff of the clinical site of any changes in your condition and well-being in a personal conversation or by phone: _____ _____.

Confidentiality

The confidentiality of information about you is protected by applicable laws and regulations. All information about you during the trial will be considered confidential. Your name and other personal information will not be included in publications related to this trial. After you (or your legal representatives) sign the patient Informed Consent Form to participate in the trial, each patient is assigned an UPI. The UPI is established by the insurer and communicated to the researcher for inclusion in the patient's medical records. Only the patient's UPI will be used in the report and trial documents. Direct access to your medical records will be provided to the clinical site staff conducting the trial, representatives of the Sponsor, and representatives of government regulatory authorities. They are required to maintain confidentiality and treat the data being studied as confidential.

Voluntary participation in the trial and refusal to participate

Your decision to participate in this trial is strictly voluntary. You make your own decision about participation and can change it at any time and stop participating in the trial without giving a reason. If you decide to stop participating in the trial, please inform your physician immediately and discuss with him/her the possibility of a final visit.

Your participation in the trial may be terminated by your physician if:

• You do not comply with the physician's orders and procedures as provided in the trial Protocol;

• The physician has decided that it is in the interests of your health and well-being to stop participating in the trial.

If new information becomes available during the trial that may affect your decision to continue participating in the trial, it will be provided to you by the physician-investigator.

If you or your relatives have any questions about this trial, you should contact your physician _____ by phone number:_____ or the authorized representative of the Sponsor, Galina Astashkina by phone: +7 (495) 287-98-07, +7-926-953-53-92 (mobile).

You can also contact the Local Ethics Committee of _____ located at _____

Chairman of the Local Ethics Committee:

_____

_____

If necessary, you may contact the following persons for additional information about the trial and the rights of trial subjects, as well as in the event of harm to health as a result of harm to health as a result of participation in the trial:

Principal Investigator:

_____

phone, e-mail_____

In addition, for any aspects of your participation in the trial, you can contact the Ethics Council of the Ministry of Health of the Russian Federation at the following address:
3, Rakhmanovsky per., Moscow, 127994, phone: +7 (495) 625-44-21.

PATIENT'S INFORMED CONSENT FORM

Me (or my legal representative), _____

residing at the address: _____

Unique patient identifier (UPI):

0	**1**	**6**	**1**	**5**	**0**	**1**	**2**	**0**	**1**	**9**													**0**	**0**	**0**	**0**	**0**	**0**		

I confirm that I have been informed about the objectives of this trial, the trial drug, the indications for its use, the method of administration, possible adverse events, as well as the possible inconveniences and risks for me when participating in the trial.

I confirm that I have had sufficient time to read and consider the information received. I confirm that all terms used to describe this trial that were unclear to me have been explained to me. I have received answers to all questions regarding my participation in this trial. I know that I have the right to stop participating in the trial at any time without giving a reason. I authorize access to my medical records by official representatives of health authorities, the Sponsor and members of the Ethics Committee.

I have received a signed and dated copy of this document. I agree to participate in the clinical trial "A randomised open-label, multicentre, parallel-group, non-inferiority trial FORPE of Fortelyzin® («SuperGene», LLC) single bolus administration and Actilyse® (Boehringer Ingelheim Pharma GmbH) bolus-infusion administration in patients with massive pulmonary embolism".

Full name:_____

Signature: _____ Date: "____"_____ 20___.

I hereby confirm that I have provided the patient with full information in accordance with the above.

Full name of the person who received consent_____

Signature: _____ Date: "____"_____ 20___.

In cases where the patient's condition does not allow him to express his will and there is no legal representative, and the need for treatment is urgent, the issue of medical intervention in the interests of the patient and his inclusion in the trial is decided by the council, and if it is impossible to assemble a council - directly by the attending (duty) physician with subsequent notification of the principal investigator, officials of the clinical site and the legal representative. If the patient is included in the trial by decision of the council, then in the future, if the patient's condition allows him to express his will, he must be informed about the trial as soon as possible and must give his consent to continue participating in the trial.

Members of the council:

_____

_____

_____

Date: "____"_____ 20___.