

Effects of intravenous sivelestat sodium on prevention of acute respiratory distress syndrome in patients with sepsis

Informed Consent Form · Informed Notice Page

Dear Madam/Sir

We will invite you to participate in a clinical trial on the prevention of acute respiratory distress syndrome (ARDS) in patients with sepsis using sivelestat sodium. This trial has been reviewed and approved by the Clinical Research Ethics Committee of Zhongda Hospital affiliated to Southeast University (approval number: 2021ZDSYLL153-P03).

Before deciding whether to participate in this trial or not, please read the following content as carefully as possible. It can help you understand the trial and why it was conducted, the procedure and duration of the trial, and the potential benefits, risks, and discomfort that participating in the trial may bring to you. If you are willing, you can also discuss with your relatives and friends, or ask a doctor for an explanation to help you make a decision.

1. Background, objectives, and design

1.1 Background

Acute respiratory distress syndrome (ARDS) is essentially an uncontrolled inflammatory response, and neutrophil inflammatory response is one of the important pathogenesis of ARDS. Neutrophils and neutrophil Elastase (NE) can cause endothelial damage, increase vascular permeability, make protein and water in plasma leak out of pulmonary vessels, and promote the occurrence and development of ARDS. The NE inhibitor sivelestat sodium has obvious protective effect on the hamster acute lung injury model induced by endotoxin and tracheal inhalation of hydrochloric acid. Sepsis is the main risk factor for ARDS. This trial observes the preventive effect of sivelestat sodium on the occurrence of ARDS in patients with sepsis.

1.2 Objectives

Clarify the effect of sivelestat sodium on the occurrence of ARDS in sepsis patients.

1.3 Design

1.3.1 Methods

This is a multicenter, prospective, randomized, placebo-controlled, and sample size re-estimated adaptive clinical trial aimed at observing the effects of sivelestat sodium on prevention of ARDS in patients with sepsis.

You or your family members will be randomly assigned to the experimental group (sivelestatin sodium group) and the control group (only containing excipient ingredients group), so the probability of you or your family members being assigned to the experimental group and the control group is 50% and 50%, respectively.

1.3.2 Trial participants and expected number of included subjects

Research participants: Zhongda Hospital affiliated to Southeast University, Nanjing Drum Tower Hospital and Xuzhou Central Hospital; Expected total number of subjects included: 238, and our center plans to enroll 80 subjects.

1.3.3 Expected duration of research and project initiation time

The longest duration of the intervention group is 7 days; The project was launched in October 2021.

1.3.4 Inclusion criteria

- (1) Adults (age equal to or more than 18 years, equal to or less than 75 years old).;
- (2) The sepsis 3.0 diagnostic criteria were met within 24 hours after admission;
- (3) The patient or family member has a full understanding of the purpose and significance of this trial, voluntarily participates in this clinical trial, and signs an informed consent form.

1.3.5 Exclusion Criteria

- (1) Patients identified with ARDS at the time of admission;
- (2) Patients who explicitly refused mechanical ventilation;
- (3) Patients with 3 or more extrapulmonary organ injuries and organ failure (single organ SOFA score ≥ 3);
- (4) Patients who need home oxygen therapy or with home mechanical ventilation (by tracheotomy or noninvasive ventilation, but excluding CPAP/BiPAP, only for patients with obstructive sleep apnoea);

- (5) Patients whose expected survival time is less than 48 hours;
- (6) Pregnant women and lactating women;
- (7) Patients with other conditions that were judged by the researcher to not be suitable for inclusion.

2. Subject Responsibility

2.1 Before you agree to participate in this trial, the researcher will ask and record your medical history, and conduct blood routine test, liver and kidney function, coagulation function, Troponin I, blood gas analysis, blood lactic acid, high-sensitivity C-reactive protein, pro Calcitonin, inflammatory factors and neutrophil Elastase, Pregnancy test (blood pregnancy or urine pregnancy), ECG, chest X-ray or chest CT examination for women of childbearing age.

You are a qualified enrollee and can voluntarily participate in the trial by signing an informed consent form.

If you are unwilling to participate in the research, we will follow your wishes.

2.2 The following steps will be followed if you agree to participate in this trial:

The subjects **do not** require additional invasive medical procedures, and only need to follow the doctor's instructions to continue intravenous use of the drugs provided by the manufacturer (either sivelestat sodium or placebo, randomly assigned) for a minimum of 1 day and a maximum of 7 days. Blood samples need to be taken on the 1st, 3rd, and 7th days of enrollment. Receive daily medication checks and cooperate with staff to keep records. On the 28th and 90th days of enrollment, researchers will arrange a telephone follow-up.

In the above treatment/examination, the prevention of ARDS by sivelestat sodium in sepsis patients is research. If you do not participate in this study, you do not need to accept the examination of neutrophil elastase project and the treatment of sivelestat sodium.

2.3 Other matters that require your cooperation

You need to cooperate with the medication according to the agreed time between the doctor and you, and undergo relevant examinations and tests at the specified time. Your

follow-up is very important because doctors will evaluate the effectiveness of research measures based on the follow-up. During the study, you cannot use other drugs (or other treatment methods that affect this study) to treat anti neutrophil elastase.

If you need other treatment, please contact your doctor in advance.

3. Subject Rights and Interests

Your participation in the trial is voluntary and the information provided is confidential. You may refuse to participate in the trial or withdraw from the trial at any time without discrimination or retaliation, and your medical treatment and rights will not be affected.

You can choose not to participate in this trial or withdraw from the trial midway. You do not have to choose to participate in this trial in order to treat your illness.

If you require other diagnosis/treatment, or if you do not comply with the research plan, or for any other reasonable reason, your doctor or researcher may suspend your participation in this trial at any time for the best interests of you.

If you withdraw from the trial for any reason, you may be asked about your use of the investigational drug. If the doctor deems it necessary, you may also be required to undergo laboratory and physical examinations. This is very beneficial for protecting your health.

If there is any important new information during the research process that may affect your willingness to continue participating in the study, your doctor will promptly notify you or your guardian.

You can stay informed of information and research progress related to this trial at any time. If you have any questions related to this study, or if you experience any discomfort or injury during the experiment, or if you have any questions regarding your rights and interests in this study, you can consult the researcher at any time.

Researcher Name:

Contact Information:

If you have any complaints about participating in this study, please contact the Clinical Research Ethics Committee of CUHK Hospital affiliated to Southeast University at 025-83272015.

4. Possible benefits of participating in research

At present, the high mortality rate, high cost, and heavy social burden of ARDS in clinical practice make it of great clinical significance to prevent sepsis patients from developing ARDS. Participating in this trial will give you the opportunity to receive new treatments, reduce the risk of disease progression and death, but may not benefit you.

5. Possible adverse reactions, risks, discomfort, and inconvenience associated with participating in research

For all clinical trials, the investigational drugs and research procedures may involve unknown risks. Any medication may have temporary or permanent side effects, which may lead to unforeseeable adverse reactions. Research drugs may not alleviate your disease condition.

Common adverse reactions of the drug in clinical trials include: increased Alkaline phosphatase (ALP) (10.3%), aspartate aminotransferase (AST) (9.5%), alanine aminotransferase (ALT) (8.6%), increased bilirubin (3.4%), decreased red blood cell count (3.4%), decreased hemoglobin (2.6%), presence of urinary protein (2.6%), increased creatinine (2.6%), increased urea (2.6%) Elevated platelet count (1.7%), decreased platelet count (1.7%), etc.

In case of liver function damage (AST, ALT, ALP or bilirubin is more than 3 times of the patient's D0 baseline value) and judged to be caused by the drug, we will immediately stop the use of the drug, and give Symptomatic treatment according to the degree of liver function damage: including ensuring liver perfusion, giving liver protection treatment, and giving blood purification treatment if necessary.

In this trial, venous and arterial blood will be drawn from your arm. There may be some discomfort and local bruising during blood collection, and there is also a potential risk of infection. In addition, there may be risks such as subcutaneous hematoma and bleeding at the blood collection site during arterial blood collection. Other very rare risks include dizziness and fainting.

During an electrocardiogram examination, small stickers will be applied to your arms, legs, and chest, and the machine will then detect your electrocardiogram activity. These stickers may cause local irritation and may cause discomfort when removed.

In blood pressure and heart rate checks, after you sit for 10 minutes, an inflatable

armband will be placed on your arm, and the machine will automatically detect your blood pressure and heart rate. Your arm may feel some discomfort due to the tightening of the armband.

In the imaging examination, you will undergo low-dose radiation examination.

If you suffer any discomfort, new changes in your condition, or any unexpected circumstances during the trial period, whether related to the trial or not, you should promptly notify your doctor, who will make a judgment and provide appropriate medical treatment.

6. Related expenses

Drugs and examinations related to this trial and the test are free (blood routine test, hypersensitive C-reactive protein, liver and kidney function, coagulation index, Troponin I, blood gas analysis, blood lactic acid, PCT, inflammatory factors, and women's Pregnancy test on the first day of enrollment (women of childbearing age), neutrophil Elastase on the first, third, and seventh days of enrollment, and chest radiographs on the third and seventh days of enrollment), The treatment and examination required for other diseases that you have merged at the same time, as well as the cost of switching to other treatments due to ineffective treatment, will not be included in the free scope.

7. About compensation

The applicant has purchased clinical trial liability insurance for this clinical study. In the event of damage related to the trial (excluding medical accidents), the applicant will bear the corresponding treatment costs and compensate in accordance with national laws and regulations. Signing this informed consent form will not harm any of your rights.

8. Confidentiality of personal information

Your medical records and information will be kept intact in the hospital. Researchers, ethics committees, drug regulatory authorities, and health commission management departments will be allowed to access your medical records. Any public report on the results of this trial will not disclose your personal identity. We will protect the privacy of your personal medical data to the extent permitted by law.

According to the principles of medical research ethics, in addition to personal privacy information, experimental data will be available for public inquiry and sharing, and inquiry and sharing will be limited to web-based electronic databases to ensure that no personal privacy information is leaked.

In addition to this trial, it is possible to reuse your medical records and pathological examination specimens in other future studies. You can now also declare your refusal to use your medical records and pathological examination specimens for other studies besides this one.

Informed consent form. Consent signature page

Declaration of Consent

I have read the above introduction to this trial and have the opportunity to discuss and raise questions with the researchers regarding this study. All the research related questions I raised have been answered, and my family and I have ample time to consider them.

I am aware of the potential risks and benefits associated with participating in this study. I understand that participating in the trial is voluntary and understand:

☐ The research has been approved by the Clinical Research Ethics Committee of the Zhongda Hospital affiliated to Southeast University.

All my information is confidential.

My privacy, medical treatment, and compensation rights have been protected.

I can consult researchers for more information at any time.

I can choose not to participate in this trial or withdraw from this trial at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

If I withdraw from the trial midway, especially due to medication reasons, I should inform the researchers of the changes in my condition and complete corresponding physical and chemical examinations, which will be very beneficial for the entire study.

If I need to take any other treatment due to changes in my condition, or if I fail to comply with the research plan, I will seek the opinions of the researcher in advance or truthfully inform them afterwards. The researcher may terminate my participation in this trial due to this or other reasonable reasons.

I agree that the drug regulatory department, the health commission management department, the ethics committee, or the applicant representative can access my research materials.

I will receive a signed and dated copy of the informed consent form.

Finally, I have decided to agree to participate in this trial and ensure that I follow the research procedures as much as possible.

I agree ☐ refuse ☐ use my medical records and pathological examination specimens for other studies other than this one.

Subject's signature:

Date:

Contact number:

Guardian signature (if applicable):

Date:

Relationship between guardian and subject:

Guardian contact phone number:

Signature of impartial witness (if applicable):

Date:

Relationship between impartial witnesses and subjects:

Contact number of impartial witnesses:

I confirm that I have explained the detailed information of this trial to the subjects, including their rights, potential benefits and risks, and answered their questions. The subjects voluntarily participated in the trial and have been provided with a signed copy of their informed consent form.

Researcher's signature:

Date:

Contact number of the researcher: