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Effects of intravenous sivelestat sodium on prevention of acute respiratory distress syndrome in patients with sepsis: study protocol for a double-blind multicentre randomised controlled trial

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ABSTRACT

Introduction Sepsis is one of the most common risk factors for acute respiratory distress syndrome (ARDS). Neutrophil elastase (NE) is believed to be an important mediator of ARDS. When sepsis occurs, a large number of inflammatory factors are activated and released, which makes neutrophils migrate into the lung, eventually leading to the occurrence of ARDS. Sivelestat sodium is an NE inhibitor that can inhibit the inflammatory reaction during systemic inflammatory response syndrome and alleviate lung injury. Therefore, we hypothesise that intravenous sivelestat sodium may prevent the occurrence of ARDS in patients with sepsis.

Methods and analysis This is a prospective, investigator-initiated, double-blind, adaptive, multicentre, randomised, controlled clinical trial with an adaptive 'sample size re-estimation' design. Patients meeting the inclusion criteria who were transferred into the intensive care unit will be randomly assigned to receive sivelestat sodium or placebo for up to 7 days. The primary outcome is the development of ARDS within 7 days after randomisation. A total of 238 patients will be recruited based on a 15% decrease in the incidence of ARDS in the intervention group in this study. A predefined interim analysis will be performed to ensure that the calculation is reasonable after reaching 50% (120) of the planned sample size.

Ethics and dissemination The study protocol was approved by the Ethics Committee of ZhongDa Hospital affiliated to Southeast University (identifier: Clinical Ethical Approval No. 2021ZDSYLL153-P03). Results will be submitted for publication in peer-reviewed journals and presented at relevant conferences and meetings.

Trial registration number NCT04973670.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is one of the first prospective randomised controlled trials applying intravenous sivelestat sodium to acute respiratory distress syndrome in patients with sepsis.
⇒ It is a prospective, double-blind, adaptive multicentre, randomised controlled clinical trial with a re-estimation of the sample size.
⇒ Appropriate sample size calculation was not possible due to the lack of available high-quality clinical data; therefore, the sample size was calculated in two stages to ensure that the calculation was reasonable, maximising the possibility of obtaining significant results and providing credible outcome data.
⇒ As the duration and distribution of infected patients are unpredictable geographically and temporally, the number of recruited patients at each centre is also unpredictable, in spite of the competitive enrolment.

INTRODUCTION

Background and rationale

Acute respiratory distress syndrome (ARDS) is a life-threatening and critical illness syndrome that is characterised by alveolar capillary injury and hypoxemia, with overall mortality rates of 40%.[1] Sepsis is one of the leading causes of ARDS,[2] and up to 6.8–38% of patients with sepsis will develop ARDS.[3 4] Despite advances in critical care management and lower tidal volume ventilation strategies,[5–7] the treatment for sepsis-induced ARDS remains supportive, and the mortality is higher than that for sepsis alone.[8] Therefore, how to prevent ARDS in patients with sepsis is of great significance.

In sepsis, the inflammatory storm produced in the body destroys the endothelial layer and induces endothelial cell leakage, and then neutrophils migrate into the alveoli[9] and can release neutrophil extracellular traps and elastase. Neutrophil elastase (NE) can cause vascular endothelial injury, increase vascular permeability and the permeability of pulmonary endothelial cells and epithelial cells, cause protein and water in the plasma to leak out of the pulmonary

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vessels, cause alveolar oedema and bleeding and promote the occurrence and development of ARDS.[9–11] It is one of the important pathogeneses of ARDS.

Studies have shown that sivelestat sodium, an inhibitor of NE, has obvious protective effects on hamster acute lung injury models caused by endotoxin, cobra toxin and hydrochloric acid inhaled from the trachea.[12–14] Clinical studies have shown that sivelestat sodium can improve oxygenation, ameliorate lung injury[15] and increase the time of ventilator weaning in patients with systemic inflammatory response syndrome-induced acute lung injury (ALI).[16] However, it is unknown whether NE inhibitors can prevent ARDS in patients with sepsis.

The median time of onset of ARDS was 2 days after admission.[17] The period from admission to the development of ARDS provides a short opportunity for the prevention of ARDS.[3] Studies have shown that the release of NE in patients with high-risk ARDS increased significantly in the early stage.[18] Therefore, it is of great clinical significance to prevent such patients from developing ARDS by inhibiting NE.

Thus, we hypothesise that intravenous sivelestat sodium in patients with sepsis within 24 hours after sepsis diagnosis might prevent the occurrence of ARDS. In this trial, we also will observe the effect of the drug on the improvement of oxygenation, 28-day ventilator-free days (VFD), 28-day time to clinical improvement, 28-day and 90-day mortality and so on.

Objectives

The main goal of this study is to determine whether sivelestat sodium has a protective effect on ARDS (Berlin definition)[19] in patients with sepsis.

METHODS AND ANALYSIS

Design and setting

It is an investigator-initiated, double-blind, multicentre, prospective, randomised, controlled clinical trial with an adaptive 'sample size re-estimation' design.

This protocol was constructed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2013 guidelines.[20] The protocol is summarised in figure 1 and table 1.

Study sites and period

This clinical trial is being conducted in the intensive care unit (ICU) of Zhongda Hospital affiliated to Southeast University of Nanjing City, the ICU of Nanjing Drum Tower Hospital and Xuzhou Central Hospital from 1 October 2021. Zhongda Hospital affiliated to Southeast University is an affiliated hospital of medical teaching and research university, which is the leader of this study.

Study participants

The study will enrol ICU patients who were admitted to the above three hospitals with sepsis. The specific inclusion and exclusion criteria are as follows.

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[21] diagnostic criteria were met within 24 hours after admission.
3. The patients or their family members fully understood the purpose and significance of the trial, voluntarily participated in the clinical trial and signed the informed consent form.

Exclusion criteria

1. Patients identified with ARDS at the time of admission.
2. Patients who explicitly refused mechanical ventilation.

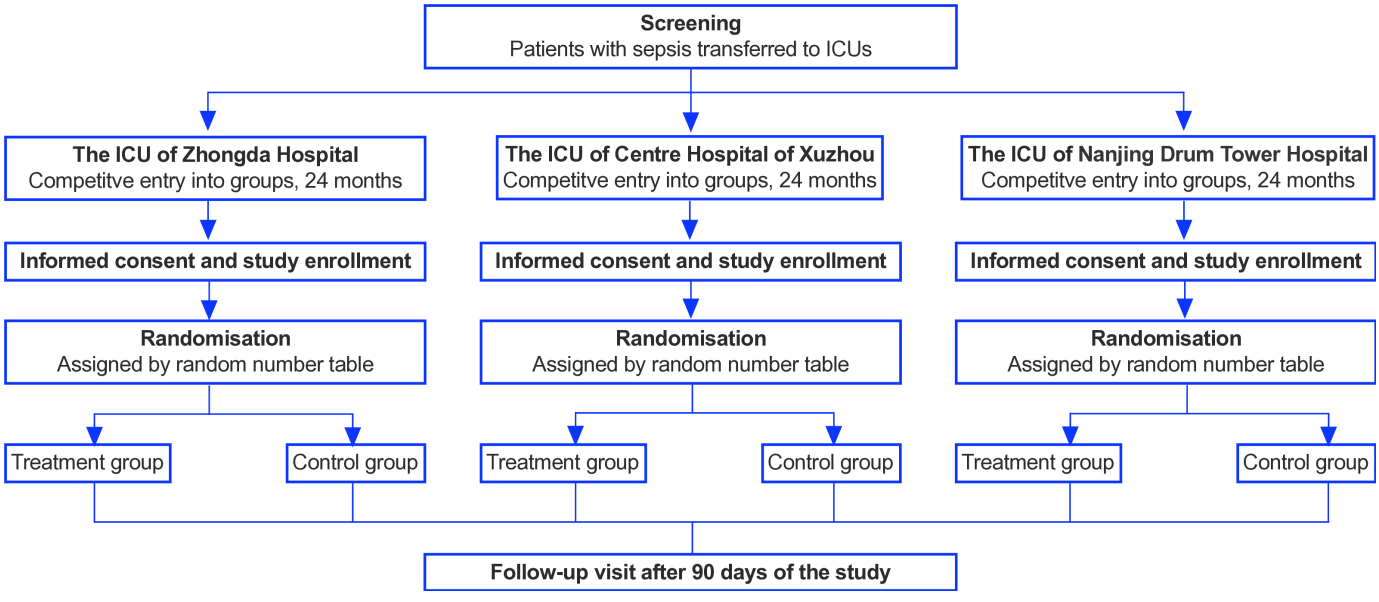

Figure 1 Study flow. ICU, intensive care unit.

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Table 1 Participant timeline

Visit	V0	V1	V2	V3	V4	V5	V6	V7	V28	V90
Time point	D0	D1	D2	D3	D4	D5	D6	D7	D28	D90
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographic data	X									
Intervention	X	X	X*	X*	X*	X*	X*	X*		
Basic disease history	X									
Physical examination and vital signs	X	X	X†	X†	X†	X†	X†	X†	X†	
Blood routine	X			X				X		
Serum chemistry‡	X			X				X		
Coagulation function	X			X				X		
Troponin I	X			X				X		
Blood gas or SpO_2/FIO_2	X	X	X†	X†	X†	X†	X†	X†		
Lactate	X			X†				X†		
CRP		X		X†				X†		
PCT		X		X†				X†		
Inflammatory factor§		X		X†				X†		
Neutrophil elastase		X		X†				X†		
Pregnancy test	X									
Chest X-ray or CT	X			X†				X†		
ECG	X			X†				X†		
SOFA score	X			X†				X†		
APACHE II score	X									
Adverse event		X	X†	X†	X†	X†	X†	X†		
Combined medication		X	X†	X†	X†	X†	X†	X†		
Ventilation free days									X	
Shock-free days									X	
Time to clinical improvement									X	
Survival									X	X

Recommendations for Interventional Trials checklist.
*Continued pumping medication if not discharged from ICU or died.
†Tested it if not died or discharged from hospital.
‡Serum chemistry includes ALT, AST, TBIL, urea, BUN, CR, ALB.
§Inflammatory factor includes IL-1β, IL-6, IL-8, IL-10, TNF-α.
ALB, albumin; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine; CRP, C reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-1β, interleukin-1β; PCT, procalcitonin; SOFA, Sequential Organs Failure Assessment; TBIL, total bilirubin; TNF-α, tumour necrosis factor-α.

3. Patients with three or more extrapulmonary organ injuries and organ failure (single organ Sequential Organs Failure Assessment (SOFA) score ≥3).
4. Patients who need home oxygen therapy or with home mechanical ventilation (by tracheotomy or non-invasive ventilation, but excluding continuous positive airway pressure/bilevel positive airway pressure, 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.

Study interventions

This study is an interventional study with two arms. The longest duration of the intervention group was 7 days. For the treatment group, 0.2 mg/kg/hour sivelestat sodium will be diluted in normal saline to a total volume of 48 mL and will be infused for 24 hours by an infusion pump. The control group will receive the same amount of normal saline containing only sivelestat sodium excipients. Except for the differences in the two drugs mentioned above,

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other critical supportive care such as anti-infection, fluid resuscitation and respiratory support were all carried out in accordance with international guidelines for the two groups. The intervention should be commenced within 1 hour after enrolment. Delivery of the assigned sivelestat sodium injection or placebo injection is supplied by Shanghai Huilun (Jiangsu) Pharmaceutical.

If the patient is transferred out of the ICU back to the general ward within 7 days, sivelestat sodium will be discontinued.

Risks, Adverse Events and Consent

As stated above, the trial is considered to be safe. First, the dose of sivelestat sodium has been demonstrated to be safe,[16] even in patients older than 60 years.[22] Second, some critically ill patients will be excluded based on the exclusion criteria. Third, the infusion rate is approximately 2 mL/hour, which is very slow. However, adverse events (AEs) and serious AEs (SAEs) must be observed and followed in accordance with the good clinical practice guidelines issued by the National Medical Products Administration of the People's Republic of China.[23]

An AE refers to any untoward medical event that occurs after a human subject receives a drug. SAEs include prolonged hospital length of stay, disability, death and so on. AEs and SAEs will be recorded during the 90 days of observation from enrolment. Either may occur during a subject's participation in the research and do not need to have a causal relationship with the treatment. The investigators will evaluate the relationship between the events and the intervention and will report it to the ethical committee and Data and Safety Monitoring Board (DSMB). Benefits and potential risks are written in the informed consent document. The patients will be informed of the purpose, intervention, benefits and possible risks of the study.

Who will take informed consent?

A member of the study team will take consent prior to the start of study activity. For patients who are unable to sign or initialise the consent form (online supplemental file 1), the consent form will be allowed to be signed and dated by his or her trustee or guardian.

Additional consent provisions for collection and use of participant data and biological specimens

As a part of the consent form process, the participants will be required to provide authorisation for extraction and use of their data. The participants will also be asked for permission to gather de-identified information that may be used for ancillary studies. Biological samples obtained for further ancillary studies are not applicable in this study.

Randomisation, allocation concealment and blinding

The randomisation sequence will be created using SAS V.9.4 (procedure 'PROC PLAN') statistical software with a 1:1 allocation ratio using a random block size of 4. The participants, care providers, investigators, outcome assessors and statisticians will be blinded to the treatment allocation results. The sivelestat sodium and placebo were manufactured by Shanghai Huilun (Jiangsu) Pharmaceutical. All of them were identical in appearance and packaging.

Researchers should not unblind the investigational drug unless it is necessary to know the information of the investigational drug for medical treatment of the subjects. When a medical emergency occurs and it is necessary to immediately identify the type of medication taken by the subject, if possible, the relevant personnel of the main researcher and sponsor must be notified as much as possible before the trial drug is unblinded. The main researcher should conduct emergency unblinding to obtain specific grouping information of the subject. If the applicant is not contacted before unblinding, they must be contacted within 24 hours after unblinding. The researcher must record the unblinding date, location, reason, unblinding person, main investigator, relevant person in charge of the drug clinical trial institution, etc, and make detailed records in the case report form. Subjects who underwent emergency unblinding were treated as dropout cases.

Data collection and management

Baseline data, including demographic characteristics, admission diagnosis assigned group, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, SOFA scores, Charlson comorbidities, source of infection and clinical information will be collected on the first day. The clinical information includes general vital signs, chest X-ray or CT, routine blood examination (red cell count, white cell count, neutrophil count, lymphocyte count, platelet count), blood biochemistry (alanine transaminase, aspartate aminotransferase, bilirubin and so on), coagulation function (prothrombin time, activated partial thrombin time, fibrinogen, D-dimer), cytokine tests (interleukin (IL)-1β, IL-6, IL-10 and so on), procalcitonin, C reactive protein (CRP), NE and blood gas analysis. The APACHE II scores, SOFA scores and clinical information will be collected on the 1st, 3rd and 7th days. The 28-day VFDs, shock-free days, length of hospital stay, time to clinical improvement, mortality and 90-day mortality will be evaluated during visits on the 28th day and 90th day.

Study outcomes

The primary outcome of this clinical trial is the development of ARDS, as defined by the Berlin criteria, within 7 days after randomisation.

The secondary outcomes include the following:

Oxygenation index (PaO_2/FiO_2) or SpO_2/FiO_2, concentration of inflammatory factors (including IL-1β, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α), concentration of NE, platelet count, concentration of CRP and SOFA score on days 1, 3 and 7 after drug administration.

The 28-day VFDs were defined as the number of days between successful weaning from mechanical ventilation

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and day 28 after study enrolment. For the patients ventilated for 28 days or more and for patients who died, the VFDs were 0.

Shock-free days (no vasopressor requirement) from day 1 to 28.

The 28-day time to clinical improvement[24] was defined as the time from randomisation to an improvement of two points (from the status at randomisation) on a seven-category ordinal scale or live discharge from the hospital, whichever came first. The seven-category ordinal scale consisted of the following categories: (1) not hospitalised with resumption of normal activities; (2) not hospitalised, but unable to resume normal activities; (3) hospitalised, not requiring supplemental oxygen; (4) hospitalised, requiring supplemental oxygen; (5) hospitalised, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation or both; (6) hospitalised, requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation or both; and (7) death.

Length of hospital stay

The 28-day and 90-day mortality.

Participant timeline

The participant timeline is presented in table 1.

Sample size and interim analysis

The project statistician calculated the sample size based on the primary outcome before starting the trial. A sample size of approximately 238 patients is required to achieve 80% power at a 2.5% one-sided α level. On the basis of the results observed in the publication by Fein and Calalang-Colucci[25] and Li *et al*,[8] the incidence of ARDS in the control group was 18~38%. Based on these data, it is assumed that the incidence rate of placebo in patients with sepsis is 30% and that of treatment is approximately 15%.

The adequacy of sample size is crucial in clinical trials. Typically, the sample size is determined based on the results of one or more external pilot studies, butt appropriate sample size calculation was not possible due to the lack of available high-quality data. So, in our study, we are uncertain about the treatment effect of sivelestat sodium, which is expected to be around 15%. Given this uncertainty, sample size adjustment may be particularly important if the trial specifications have been made on preliminary and/or uncertain information. In our approach, we prospectively plan modifications to the sample size based on interim estimates of treatment effect for sivelestat sodium and placebo. An interim analysis will be performed when the recruitment rate reaches 50%. If strong evidence of effectiveness is observed with a p value<0.00258 (one-sided), the trial will be stopped early. Otherwise, if the conditional power (CP) is greater than 80%, the trial will continue as planned, and the sample size will remain unchanged. However, if the CP is less than 80%, we will re-estimate the sample size and increase it to ensure the statistical power of the trial.

The project statistician is responsible for authorising members of the Statistical Analysis Center (SAC) to access unblinded data and prepare reports for the DSMB. Members of the SAC will not be involved in the conduct of the study, other than preparation for and attendance at DSMB meetings. The sample size re-estimation will be conducted by an independent statistician based on the actual effect size in the interim analysis. The interim analyses lead to an inflation of the type I error, and the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary was used to control type I error. If no more subjects are needed, early termination will be executed with the one-side 0.00258 nominal significance level.

Recruitment

Patient recruitment is currently being conducted in the three centres. The estimated recruitment in each centre is as follows: Zhongda Hospital, School of Medicine, Southeast University (80 participants); Nanjing Drum Tower Hospital (80 participants) and Xuzhou Central Hospital (80 participants). Recruitment started on 1 October 2021 in Zhongda Hospital. As of 31 March 2023, we had already enrolled 78 patients. There is no specific strategy to promote the rate of patient recruitment. Based on the results of the interim analysis, we will decide whether to terminate the trial or continue or add subcentres.

Statistical analysis

Statistical analysis will be performed using SAS V.9.4 statistical software. Continuous variables will be described using mean, SD, maximum, minimum, median, upper quartile (Q1) and lower quartile (Q3). Qualitative variables will be expressed using frequency and percentage. Two-sample t-tests will be employed for comparisons between the treatment groups when the data are normal and the Wilcoxon rank-sum test will be used for skewed distributions. X^2 or Fisher's tests will be used for categorical data and the Wilcoxon rank-sum test will be used for ordinal data. Significance tests will be two-tailed, with a statistical probability of p<0.05. The two-stage combination of primary outcome will be analysed by Cui-Hung-Wang (CHW).[26]

Primary and secondary analysis

The primary outcome, the incidence of ARDS, between the two study groups will be compared using the CHW method. The primary analysis of the primary endpoint will be performed without adjustment for baseline covariate imbalances using an intention-to-treat set and a per-protocol set. A sensitivity analysis of the primary endpoint will be performed after adjusting for baseline covariates, including sex, age, group assignment, source of infection and severity of illness. Last observation carried forwards imputation will be used for missing data. Planned exploratory subgroup analyses will be performed to investigate

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whether the treatment effect is modified by different initial baseline covariates.

Secondary binary outcomes between the two study groups, except for safety events, will also be compared using χ^2 or Fisher's tests. Two-sample t-tests or Wilcoxon rank-sum tests will be used for quantitative data. Safety analysis will be performed in a safety set, which is defined as a subset of subjects who were randomised and received at least one treatment.

Data safety monitoring

An independent DSMB comprised of two academic intensivists outside the study who are experienced in conducting clinical trials in critical illness is monitoring the progress and safety of the trial. The DSMB is able to pause the trial to investigate or give suggestions on any potential safety issues to improve the study design and implementation.

Patient and public involvement

There was no patient and/or the public involvement in the design, or conduct, or reporting, or dissemination plans of this protocol.

Ethics and dissemination

The study protocol was approved by the Ethics Committee of ZhongDa Hospital affiliated to Southeast University (identifier: Clinical Ethical Approval No. 2021ZDSYLL153-P03). Any changes in the study will generate synchronously protocol amendments, which will be submitted for approval to the Ethics Committee/institutional review board for filing in a timely manner. The changes will only be implemented after approval by the ethical committee. Once approved, the amendments will be circulated to the other study sites and ClinicalTrials.gov will be synchronously updated about any major changes.

This study results will be submitted for publication in peer-reviewed journals and presented at relevant conferences and meetings. The primary outcome of the study will be published as the first article and additional results derived from the data could be published in separate articles.

DISCUSSION

Many recent studies have found that the elastase released by neutrophils is involved in the degradation of the main components of the extracellular matrix, a process that is closely related to lung injury.[22] Inhibition of NE can improve the clinical outcome of patients with ALI, such as increasing the ventilator-weaning rate and ICU discharge rate.[16]

Sivelestat sodium is a selective NE inhibitor that can reduce pulmonary haemorrhage and exudation and reduce pulmonary oedema mainly by inhibiting the aggregation, adhesion and infiltration of neutrophils.[9] It reduces the release of inflammatory factors such as IL-8 and TNF-α, inhibits inflammatory reactions and improves symptoms of lung injury.[27] At present, sivelestat sodium has been widely used in the clinic, mainly for patients with ALI/ARDS.[22 28 29]

To the best of our knowledge, this is one of the first randomised controlled trials using sivelestat sodium to prevent the occurrence of ARDS in patients with sepsis. The treatment of ARDS is very limited, including low-tidal-volume ventilation, prone positioning, conservative fluid strategies and ECMO, but the effect is limited.[30] ARDS brings a heavy medical burden to society.[31] Therefore, this trial is of great significance, could save lives and allow for a lower economic burden. Sivelestat sodium is expected to inhibit sepsis inflammation, prevent ARDS and reduce mortality for patients with sepsis. In addition, it may also provide a basis and reference for the treatment of other diseases with similar mechanisms.

However, our study design also has some limitations. First, the upper age limit of this study is 75 years old. It is unknown whether patients with sepsis over 75 years old have the same result. Further research may be needed for these patients in the future. Second, we included patients with sepsis transferred to the ICU, and there may be selection bias for patients with sepsis not transferred in time. In addition, the patients with sepsis transferred from other hospitals may have had ARDS, and these patients were excluded from the study.

Trial status

The trial is currently ongoing at three sites (Zhongda Hospital, School of Medicine, Southeast University; Nanjing Drum Tower Hospital; and Xuzhou Central Hospital) in China. Enrolment started in October 2021 in Zhongda Hospital. Currently, all three sites are actively screening for patients. As of 31 March 2023, we had already enrolled 78 patients. The protocol version is 1.3 (12 October 2021).

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Contributors LL and YY are the principal investigators. SM, CL, ZG, JX, HQ, YY and LL designed the study protocol. SM wrote the manuscript. All authors contributed to revising the manuscript. The authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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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: