Informed Consent Form

INFORMATION TO PARTICIPANTS

NAME OF STUDY:	A Randomized, Double-Blind, Placebo-Controlled, Four-Arm, Parallel-Group, Proof of Concept, and Dose-Finding Adaptive Phase 2a/2b Study to Investigate the Safety, Tolerability and Efficacy and Effect on Quality of Life of Human Recombinant Alkaline Phosphatase in the Treatment of Patients With Sepsis-Associated Acute Kidney Injury.
STUDY NUMBER:	AP-recAP-AKI-02-01
STUDY SPONSOR:	AM-Pharma B.V. Rumpsterweg 6 3981 AK Bunnik The Netherlands
STUDY DOCTOR (INVESTIGATOR):	[Investigator Name] [Site Address] [Office Hours Tel] [Out of Hours Tel]
[ETHICS COMMITTEE (EC) or INVESTIGATIONAL REVIEW BOARD (IRB):]	[EC/IRB Name] [EC/IRB Address] [Office Hours Tel] [Out of Hours Tel]

Why are you receiving this information?

You are, or if you are the legal accepted representative the patient is, invited to take part in a clinical research trial. In the following text 'You' refers to the patient concerned. In case the patient is not in a condition to consent, you as a legal accepted representative of the patient will be informed about the trial and consent to participation on behalf of the patient, according to local regulations. When the patient is well enough he/she will receive information about the trial and a new consent will be obtained.

Before deciding on participation, it is important that you understand why the trial is conducted and what is expected of a patient, as well as the benefits, risks and inconveniences that may be related to participating in this trial. The following information describes the study and your role as a possible participant. Take your time reading the information and don't hesitate to ask the study doctor any questions to ensure that you are able to make an informed decision as to whether to participate.

This document is called an informed consent form. It has information to help you decide if you want to take part in this study. It explains the purpose, procedures, your responsibilities, benefits, risks and discomforts of the study, and your right to stop being in the study at any time without penalty or loss of benefits that you normally receive. It also explains how your medical information will be used and who may see this information. If you decide to take part in this study and allow your medical information to be collected, used and shared with certain

persons involved in the study, you will be asked to sign this form. If you do not want your information collected and do not sign this document, you will not be able to take part in this study.

[This trial has received a positive opinion by an Ethics Committee and the Health (regulatory) authorities according to regulations.]
These committees are set up to protect the rights and well-being of people participating in research studies like this one.

What is the purpose of this clinical research study?

Sepsis is a condition that occurs when the body reacts to infectious agents in the blood stream (blood poisoning).

Sepsis often leads to multi-organ dysfunction and the kidney is one of the organs frequently afflicted.
Currently, there is no single drug approved for the treatment of sepsis-associated acute kidney injury (SA-AKI) and dialysis (renal replacement therapy, RRT) is the only supportive treatment option available for AKI.
The procedures performed for this study will be performed in addition to your standard of care. If you have any questions about any of the procedures, you should ask the study doctor or study staff involved in this study.

Alkaline phosphatase (AP) is present in many human cells or organs and helps the body to fight infection and to reduce body-cell damage.

A recombinant (combined genetic material) human AP (recAP) was developed by AM-Pharma which is given to patients via intravenous (IV) infusion. The purpose of this study, which involves research, is to determine if recAP is safe and effective in improving renal function of patients with SA-AKI.

The purpose is also to determine the therapeutic dose(s) (amount of medicine that will be safe and effective) of recAP and to investigate the effect on your quality of life.

RecAP has previously been tested in animals and in 51 healthy volunteers and the results show safety and non-toxicity of the drug. RecAP is an add-on treatment to your other medication and the standard of care available.

It is expected that approximately 315 subjects will be enrolled in this study in Europe and the United States of America.

What procedures are involved?

After signing this informed consent form, the screening assessments may start. In order to ensure the start of trial treatment without delay, informed consent will be obtained as early as possible.

The trial period is 90 days including daily assessments on day 1 through day 7. You will receive treatment on day 1 through day 3, weekly assessments on days 14, 21 and 28 and follow-up visits on day 60 and day 90.

If you have been diagnosed with sepsis and SA-AKI, you are very sick. According to standard of care, your doctor will take several blood and urine tests and perform other procedures/tests to monitor your progress and provide the best available treatment to you. During the course of the disease, your doctor will continue to take tests that he/she thinks are necessary. Your condition will be monitored closely while in the intensive care unit (ICU) and any medication you receive in addition to trial medication will be recorded.

If you decide to participate in this clinical research trial, extra tests and blood and urine samples will be needed. The care in the study does not replace your regular medical care. If you are not familiar with any of these procedures, please ask your study doctor to explain this further.
Your heart rate, temperature, breathing rate, body weight, height and blood pressure will be recorded. You will have electrocardiograms (ECG, relating to heart) and you will be asked to answer questions about your general health status (via EuroQOL five dimensions questionnaire (EQ-5D™) - one of the most commonly used questionnaires to measure health-related quality of life). Urine samples will be collected and your fluid balance will be recorded. Approximately 178 - 208 mL (35-42 teaspoons) of blood will be collected for the entire trial.

Your blood and urine samples will be sent to the PPD Global Central Laboratory [in either Highland Heights, Kentucky, USA or Brussels, Belgium] for further processing and analysis. A part of this blood sample will be retained for additional required analyses up to 1 year after the end of the study unless a specific authorization is given by AM-Pharma to destroy the samples. Other blood samples will be sent to PRA Bioanalytical Laboratory (Assen, The Netherlands) for further testing.

All identifiable samples will be handled in a manner to maintain your confidentiality and will be labelled with a code number and kept in locked storage. Only your study team will be able to link your samples with your identity. No one working with your samples will know your identity.

Screening Assessment and Baseline

Once you (or your legally acceptable representative) have signed the informed consent document, the procedures will take place:

Screening

- Information about yourself, such as name, race (for clinical trial purposes only) and date of birth (if permitted by local regulations) will be collected.
- Your previous and present medical history, together with any medication or therapy you have recently received will be reviewed.
- The diagnosis of AKI will be confirmed.
- In case of liver disease the Child-Pugh score will be taken to exclude chronic liver disease.
- A Pregnancy test will be performed, if appropriate, as it is important to confirm that you are not pregnant.
- Recent microbial and blood test results (if available) will be reviewed.
- A blood sample (6 mL ~ 1 teaspoon) will be taken for local laboratory analysis and decreased urine output will be confirmed.
- Your Body Weight and Height will be measured or estimated.
- Your study doctor will make sure you meet the inclusion criteria for this trial.

Baseline

If you are found eligible for the trial and meet all requirements for participating in the trial (these requirements will be fully explained to you by your study doctor), the following procedures will be performed prior to treatment with recAP:

- Vital signs will be collected including temperature, heart rate, breathing rate, oxygen saturation and blood pressure.
- A physical examination will be performed.
- A urine sample will be taken for laboratory analysis and the urine volume will be determined.
- 12 mL (~ 2 tablespoons) of blood will be taken.
- An ECG (electrocardiogram that monitors your heart function) will be performed.
- The "Acute Physiology And Chronic Health Evaluation II" (APACHE II) and the "Simplified Acute Physiology Score 2" (SAPS-2) will be done to document the severity of your disease.
- The "Sequential Organ Failure Assessment" (SOFA) score will help your study doctor to monitor your general health status and organ dysfunction.
- You will be asked to complete the quality of life questionnaire (EQ-5D™) to document your general health status.

Day 1-3 - the first 72 hours in the clinical research trial

RecAP will be administered to you once per day via a 1-hour intravenous (IV) infusion – on days 1, 2, and 3. Three different dose regimen of recAP are to be studied and you may either receive one of these three doses (0.4 mg/kg (low dose), 0.8 mg/kg (mid dose), 1.6 mg/kg (high dose)) or placebo (a dummy treatment that contains no active ingredients). If the most effective dose has not yet been determined, since the analysis of the data of the first 120 patient has not yet been finalized, you will be assigned by chance to one of the four groups. Your chances of receiving recAP in one of the three doses are 75% and for receiving placebo are 25%.

If the most effective dose has been determined by a group of experts based on the results of the first 120 patients, you will be assigned to the second part of this study, where a total of 170 patients will either receive the most effective and tolerable recAP dose or placebo. Your chances of receiving recAP in this study period are 50%.

Neither you nor your study doctor will know which treatment you are taking.

During these three treatment days the following procedures will be performed:

- Vital signs will be collected including temperature, heart rate, breathing rate, oxygen saturation and blood pressure up to 6 hours after receiving study medication.
- A physical examination will be performed.
- An ECG to monitor your heart function will be done on day 3.
- And the SOFA score will monitor your general health status and organ dysfunction.
- The amount of oxygen in the blood will be measured.
- A urine sample will be taken for laboratory analysis and the Urine volume will be determined.
- 6 mL (~ 1.2 teaspoon) of blood will be taken each day.

Day 4-28

After recAP or placebo treatment has ended, the following procedures will be performed:

- Vital signs will be collected once daily including temperature, heart rate, breathing rate, oxygen saturation and blood pressure on days 4 through 7, day 14, day 21 and day 28.
- A physical examination will be performed on days 4 through 7, day 14, day 21 and day 28.
- An ECG to monitor your heart function will be done on day 14.
- And the SOFA score will monitor your general health status and organ dysfunction on days 4 through 7, day 14, day 21 and day 28.
- You will be asked again to complete the quality of life questionnaire (EQ-5D) at discharge from the ICU.
- The amount of oxygen in the blood will be measured on days 4 through 7, day 14, day 21 and day 28, if invasively ventilated (a machine is assisting with your breathing).
- A urine sample will be taken for laboratory analysis and the urine volume will be determined.
- 6 mL (~ 1,.2 tablespoons) of blood will be taken on days 4 through 7, 12 mL (~ 3 teaspoons) on day 14 and day 28, 6 mL (~ 1,2 ttablespoons) on day 21.

Day 60 and day 90

These visits are Follow-up visits and your study doctor will ask you to return (if you have been discharged from the ICU / hospital). The following procedures will be performed:

- A urine sample will be taken for laboratory analysis (day 60 & 90).
- 4 mL (~ 1 tablespoon) of blood will be drawn (day 60 & 90).
- You will be asked again to complete the quality of life questionnaire (EQ-5D) on day 90.
- Your study doctor will document your need for chronic dialysis.

What is expected from you?

When deciding you want to participate, consider if you are able and willing:

- To follow the study rules
- To commit the time required to keep appointments, especially for the follow-up visits at day 60 and day 90
- If your participation in the study ends prematurely (or before the end of your time in the study), your study doctor will ask you to complete the Day 28 procedures and return at day 90 for an adequate safety follow-up
- To tell the study doctor truthfully about your complete medical history.
- To report any new problems, illnesses, injuries, visits to the hospital, medical procedures or changes in medication during the study (especially after you leave hospital and during the day 60 and day 90 follow-up visits). It is very important that you report these events as quickly as possible to the study staff.

What are the potential risks and discomforts?

All drugs may cause certain side effects and discomforts. Previous experience with recAP in 51 healthy volunteers does not show any serious side effects and toxicity (the degree to which a substance can damage an organism). Minor discomforts, such as temporary dizziness and mild reactions, were reported, but there may be other side effects and discomforts that are not yet known.

Most of the blood tests will be taken from catheters (tubes) which are already in place so it will not cause you any additional discomfort. When a sample of your blood is drawn by using a needle, you may experience some temporary discomfort, bruising, swelling and/or, in rare circumstances, infection at the needle site. Please tell the study doctor or study staff if you do not feel well after having your blood drawn.

An ECG is an electrical tracing of the heart used to monitor heart function. Small wires are attached to your body using adhesive patches in several places. You may experience temporary discomfort (pulling on the skin/skin hair) during removal of the adhesive patches. After you have an ECG, you may have mild irritation, slight redness, and itching at the places on your skin where the recording patches are placed.

Are there any reproductive risks?

Women: If you are a woman of childbearing potential and you are planning to become pregnant in future, participation in this study may pose a theoretical risk. The safety of this drug during pregnancy was not tested previously in either human or in animal studies. Because alkaline phosphatase is present in the human placenta it is theoretically possible that you could develop anti-placental antibodies after receiving study drug. Such antibodies could interfere with your ability to have a successful pregnancy in future. While development of anti-drug antibodies was not seen to date in human studies, the safety experience with this drug is limited to only 37 subjects who received study drug and no data is available regarding effect of the drug on human reproduction. If you are considering pregnancy in future you are advised to discuss this issue further with your GP and/or the Principal Investigator. Therefore, it is not known if the study medication may affect an unborn child or nursing infant. For this reason, if you are breast-feeding, pregnant or plan to become pregnant within 28 days of enrolling into this study, you may not participate in this study. If you are able to become pregnant, you must use an acceptable method of birth control for the entire study duration of 90 days.

Men: It is not known if the study treatment may affect your sperm or an unborn child. For this reason, you must use an acceptable method of birth control for the entire study duration of 90 days.

Birth Control: An adequate barrier method or hormonal method of contraception should be used. It is important that you tell the study doctor immediately if you or your partner becomes pregnant during the study. The doctor will talk with you about what you should do.

What are the benefits of participation in the study?

It is unknown if this research trial will benefit you personally. In the event that recAP is successful, the information obtained from the trial may help to find a more effective treatment for patients with sepsis-associated acute kidney injury (SA-AKI). It is possible that you may not personally benefit from your participation in this study. However, by taking part, you will provide new information that may benefit other patients in the future.

Are there any alternative treatments?

Currently, no alternative treatment for SA-AKI is available.

Will you be informed if new information becomes available during the study?

Your study doctor will inform you or your legal representative in a timely manner of any new information learned during the study that may affect your willingness to continue your participation.

Who can you contact with further questions?

You may ask questions about this consent form or the study at any time (before or during the study). If you have additional questions, or experience a research-related injury, contact the study doctor using the details provided in the table on the first page of this information sheet.

If you have a complaint or question about your rights as a research subject, you may contact the [Ethics Committee (EC) or Institutional Review Board (IRB)] using the details provided in the table on the first page of this information sheet. This is a group of scientific and non-scientific individuals who review research studies with the safety and welfare of research subjects in mind.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. This web site only shows data in English, but you can request information from the study staff at any time and have access to data that are publicly available.

What happens if you change your mind?

Your participation in this study is voluntary. You do not have to take part, and you may discontinue your involvement at any time without giving any reason and without penalty or loss of benefits to which you are otherwise entitled. If you decide to leave the study before the last study visit, tell your study doctor and follow his/her instructions. It may be helpful if you could explain your reasons. You may receive standard treatment and no prejudice will be shown towards you for medical care or participation in future research.
Information collected up to when you left the study will remain in the database, but no further information will be collected. You should however be aware that samples and recordings obtained before your withdrawal may already be analysed (in this case, no new data will be added to the database). You (or your legally acceptable representative) can request destruction of collected samples that would otherwise remain in storage.

In addition, your study doctor or the sponsor may withdraw you from the study for your own safety, even if you wish to continue to participate. This might be if you do not follow the study rules or if you experience study-related injury. You may also be withdrawn from the study due to laboratory abnormalities, clinical events, if you have another illness which – in the opinion of your study doctor – shows that continued participation in this study is not in your best interest.

If your participation in the study is stopped early, you may be asked to complete the end of study procedures (such as a final medical examination and laboratory tests) for your own safety.

After you have withdrawn from the study before its conclusion, your study doctor (or appointed delegate) may try to learn your long term health status for a period of not more than 3 months, by accessing your hospital records, or publicly available sources such as national registries, newspaper obituaries and social networking websites. Attempts may also be made to contact you or your relatives to gather this information. If you do not want this information about you to be collected, you may record your objection with your study doctor at any time.

EMEA:

Are there any costs if you decide to participate?

You will not receive payment for participating in this study, but the study drugs will be made available to you at no charge and you will not be required to pay for any study procedures. You may be reimbursed for any

reasonable travel expenses (car (mileage)/bus/train/taxi fares) you pay as a result of taking part in this study if you give a receipt.

Who is funding this research?

AM-Pharma B.V. (a pharmaceutical company) will be organizing and funding this study. AM-Pharma B.V will pay your study doctor and/or the study site to cover their costs of conducting this study. If applicable, your study doctor will disclose to you any financial links or other interests that he/she may have to the Sponsor.

Are you insured when you participate in the study?

If you are injured because of your participation in this study, you will be entitled to receive compensation in accordance with [national] legislation. Your study doctor will explain how you can obtain a copy of these guidelines.

How will your confidentiality be respected and the privacy of your personal information maintained?

You have the right to control the use and disclosure of your personal information. Basic personal information will be recorded including your name, contact details, gender and weight, as well as information on your medical history, and clinical data collected about your participation in the study. The following people may also access these records:

- Study monitors and auditors, who may work for AM-Pharma B.V. or its authorized representatives, who check that the study is being performed correctly and that the information collected about you is accurate;
- Ethical committee that approved this study and ensures that your rights and well-being are safeguarded;
- National and international regulatory authorities involved in keeping research safe for participants.

All personnel accessing your records are required to respect your confidentiality at all times.

To ensure privacy, your name and other identifying information will not be attached to records or samples release for research purposes. Instead, you will only be identified by a code. Only the study doctor and authorized personnel will be able to connect this code to your name, by a list that will be kept securely by the study site for "[insert retention period]" years. Your coded data will be forwarded to AM-Pharma B.V. and its service providers for activities related to the study e.g. laboratory analysis. It will be transferred into a computer database and processed to allow the results of this study to be analyzed and reported or published. If the results of the study are published, your identity will remain confidential. A list of companies to whom your coded information is transferred is available from AM-Pharma B.V. via your study doctor.

Under data protection law [identification of national law] your study site and AM-Pharma B.V. shall be jointly responsible as 'controllers' for ensuring that your information is safeguarded. You have the right to access, through your study doctor, all the information collected about you and, if applicable, ask for corrections. But, in order to protect the scientific integrity of the study, the treatment you received in this study needs to remain unknown (= blinded) until the study data is analyzed. Recipients of your coded information may be in countries that do not have data protection safeguards and rights. AM-Pharma B.V. and its authorized representatives, and regulatory authorities, shall anyway seek to maintain confidentiality within the limits of local laws in these countries.

If you should withdraw from the study, data collected prior to your withdrawal may still be processed along with other data collected as part of the study. Normally no new information will be collected for the study database

unless you specifically consent to that. However, the law does require that any side effects you may suffer are documented and reported. To complete the study findings, your 90 day long term health status may also be recorded (unless you object). You have the right to require that any previously retained samples are destroyed.

What will happen to your data?

This clinical study may only be performed by collecting and using your medical information. Data protection laws give you the right to control the use of your personal information. Therefore, by signing this form you specifically authorize your information to be checked, transferred and processed as follows:

- The authorized representatives of AM-Pharma B.V., the Ethics Committee and regulatory authorities' inspectors may review your medical information by direct access to your medical records.
- Study data, including your coded medical information, may be used and shared for legitimate study and scientific purposes, including if you do not object, for future use in medical or pharmaceutical research.
- Study data may be transferred to other countries for processing, including countries not covered by the data protection legislation.

NORTH AMERICA:

Are there any costs if you decide to participate?

The study drugs will be made available to you at no charge and you will not be required to pay for any study procedures. You or your insurance company may be billed for any standard medical care that is not required for the research study.

Is there a payment if you decide to participate?

You will not receive payment for participating in this study, but the study drugs will be made available to you at no charge and you will not be required to pay for any study procedures. You may be reimbursed for any reasonable travel expenses (bus/train/taxi fares) incurred as a result of taking part in this study on production of a receipt.

Will you receive compensation if you are injured as a result of the study?

If you are injured because of your participation in this study, treatment for the injury will be made available through [name of physician] and [institution]. The sponsor will pay the costs of this treatment not paid by your medical insurance. No other payment is available from the sponsor or the study doctor in the event of injury. You are not waiving any legal rights by signing this form, accepting medical care or accepting payment for medical expenses.

Will the personnel involved in the study receive any payment?

The [investigator] receives payment from AM-Pharma B.V. (a pharmaceutical company), who is the sponsor of this study.

What will happen to your data?

This research study may be performed only by collecting and using your medical information. Your study records will be kept as confidential as possible. Only a number will be used to identify you. You will not be personally identified in any reports or publications that may result from this research study.

Because of the research goals of this study, however, your study records cannot be kept completely confidential. The sponsor of this study is AM-Pharma B.V.

The study personnel, the sponsor and its agents and PPD will need to review the medical information collected from you for use in this study in order to accurately record information for this study. In addition, in order to review the study findings, the U.S. Food and Drug Administration (FDA) and other regulatory agencies may review your medical records. The following sections provide a specific description of how your information will be used and disclosed if you participate in this research study. By signing this consent form, you are authorizing such access. If you do not sign this form to authorize access, you will not be able to participate in this research study.

The medical information that will be collected from you if you participate in the study includes:

- Information obtained from procedures to determine your eligibility to participate in the study, including a routine medical history, physical exam, electrocardiogram (ECG), and blood and urine tests.

- Information that is created or collected from you during your participation in the study, including the results of the electrocardiogram (ECG), and blood and urine tests and any other procedures performed during the study.
- Information contained in your underlying medical records related to your medical history and treatment.

The above information may identify you by name, address, telephone number, social security number, health plan number, study number, date of birth, dates relating to various medical procedures, and/or other identifying information.

If you sign this form and participate in the study, the study personnel will be authorized to use the information described above to carry out the purposes of the research study. The study personnel will also be authorized to disclose the information described above to the following parties involved in the research study:

- AM-Pharma B.V., PPD or other agents designated by AM-Pharma B.V. to collect or review study data for verification of study procedures and/or adverse event reporting.
- The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) that oversees the research study at your site.
- Government regulatory agencies including the FDA.

Once your information is disclosed to the study sponsors, its agents, the IRB/IEC or government agencies as described above, there is a potential that your medical information will be re-disclosed and will no longer be protected by US federal privacy regulations. In addition to disclosures to the entities identified above, PPD may further electronically disclose your coded health information to others involved in the research study, such as:

- To laboratories or offsite testing facilities for clinical tests required by study protocols.
- To approved offsite storage facilities or cloud service providers to meet study record retention and storage requirements.
- To study AM-Pharma B.V. who directs the medical research studies.
- To other third parties contracted by PPD and/or AM-Pharma B.V. to provide services related to studies.

The study data may be transferred to other countries for processing, including countries not covered by data protection legislation. The laws of your state may provide further protection.

While the study is in progress, your access to your study records will be temporarily suspended. You will be able to access your information when the research study is completed. You have the right to see and copy the medical information collected from you in the course of the study for as long as that information is maintained by the study personnel and other entities subject to federal privacy regulation.

Study data, including your coded medical information, may be used and shared for pharmaceutical research purposes related to this study. This authorization has no expiration date. In signing this form, you authorize the use and disclosure of your information for purposes of the study at any time in the future.

☐ By checking this box, you additionally consent to the use of your coded medical information, in future medical or pharmaceutical research.

You may withdraw your authorization at any time by sending a written request to [insert name of responsible study personnel] at [insert address]. If you withdraw your authorization, data collected prior to your withdrawal may still be processed along with other data collected as part of the study. Normally no new information will be collected for the study database unless you specifically authorize that. However, the law does require that any side effects you may suffer are documented and reported. To complete the study findings, your long term health status may also be obtained from public sources.

Informed Consent Form

Statement of Consent

- I have read and understand the statements in this informed consent form
- I have had the opportunity to ask questions and I am satisfied with the explanations provided
- I voluntarily agree to take part in this study
- I understand that I and/or my legal representative will receive a copy of this signed and dated written consent form

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Subject

Printed Name Signature Date/Time of signature)

Legally Authorized Representative

Printed Name Signature Date/Time of signature)

Witness (if applicable)

Printed Name Signature Date/Time of signature)

Independent Physician (if applicable)

Printed Name Signature Date/Time of signature)

- I have presented the study and answered the subject's questions
- I will give the subject/legal representative a copy of this signed and dated Informed Consent

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Presenter (Investigator/Delegate)

Printed Name Signature Date / Time of signature)