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.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44174

Source
ToetsingOnline

Brief title
AP-recAP-AKI-02-01

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
acute kidney injury, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: AM-Pharma B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Human Recombinant Alkaline Phosphatase, Sepsis-Associated Acute Kidney Injury

Outcome measures

Primary outcome

The primary endpoint is the area under the time-corrected endogenous creatinine

clearance curve from Day 1 to Day 7 i.e. AUC1-7.

Secondary outcome

The key secondary endpoint is RRT incidence during the period Day 1 (after

first treatment) to Day 28, inclusive.

Study description

Background summary

As there are no guidelines for the development of drugs for the indication SA-AKI, the current design was identified as optimal by a group of leading global experts in AKI and sepsis, and subsequently was discussed (and agreed) with European and US regulatory agencies. Therapeutic application of recAP is predicted to have potent anti-inflammatory and tissue-protective activity in patients suffering from AKI. More information can be found in the 'rationale'

in the protocol synopsis and in the introduction in the protocol.

Study objective

The primary objectives of the study are as follows:
• To investigate the effect of recAP on renal function and related clinical parameters in patients with SA-AKI.
• To determine the therapeutic dose(s) of recAP to support the pivotal Phase 3 program.

Secondary objectives
• To investigate the safety and tolerability of recAP in patients with SA AKI.
• To investigate the pharmacokinetics (PK) of recAP in a subset of patients with SA AKI (in the first 120 patients from Part 1 only).
• To investigate the immunogenic potential of recAP in patients with SA AKI.
• To investigate the effect on quality of life (using the EuroQol, EQ-5D).

Study design

This is a randomized, double-blind, placebo-controlled, 4-arm, parallel-group, proof-of-concept, and dose-finding adaptive Phase 2a/2b study.
A minimum of 290 patients with SA-AKI will be enrolled in the study. The study involves 2 parts (Part 1, Part 2) with an interim analysis between the parts, with continued recruitment during this interim analysis. Of the 290 planned patients, at least 120 patients will enroll in Part 1 and 170 patients will enroll in Part 2 with an estimated 50 patients during the interim analysis. Patients enrolled during Part 1 and during the interim analysis will be randomly assigned to receive, by 1-hour intravenous (IV) infusion, either placebo (Part 1; n1 = 30) or one of 3 different doses of recAP (Part 1; n1 = 30 in each dosing arm; i.e., 0.4 mg/kg [250 U/kg], or 0.8 mg/kg [500 U/kg], or 1.6 mg/kg [1000 U/kg]) using a 1:1:1:1 allocation ratio. Patients will receive study drug by 1-hour IV infusion once daily for 3 days (Days 1, 2, and 3). The interim analysis on the primary endpoint will be performed on all data collected after the 120th patient of Part 1 has completed the Day 7 visit of the study to select the dose to be administered in Part 2. The dose chosen will be the optimal dose of recAP on the primary endpoint in Part 1, provided there are no safety issues with that dose as judged by the DMC. In Part 2, patients will be randomly assigned to receive, by 1-hour IV infusion, either placebo (n2 = 85) or the dose of recAP (n2 = 85) selected during the interim analysis. Patients recruited during the interim analysis period to the dose selected in Part 2 will form part of the Part 2 populations, but those recruited to the doses that are not selected will be included in the Part 1 population.

Intervention

Study drug will be administered by 1-hour IV infusion as soon as possible on

Day 1, and on Days 2 and 3 at 24 ± 1 hour after the previous drug administration, by trained staff in the ICU or intermediate care unit. Patients randomly assigned to receive recAP in Part 1 or during interim analysis will receive one of the following 3 doses of recAP: 0.4 mg/kg (250 U/kg), 0.8 mg/kg (500 U/kg), or 1.6 mg/kg (1000 U/kg). Patients will receive study drug by 1-hour IV infusion once daily for 3 days (Days 1, 2, and 3). At the start of each drug administration, the exact volume of recAP or placebo to be administered to each patient will be calculated on the basis of the patient*s weight. Patients weighing between 95 to 115 kg will receive the same dose as that for patients weighing 100 kg. A medication preparation instruction sheet including a table with weight ranges and pre-calculated corresponding volumes will be provided. The maximum weight is limited to 115 kg (253 lb). The volume of the matching placebo medication will be identical to the volume the patient would receive if randomly assigned to recAP.

Study burden and risks

Patients will be asked to answer questions about their general condition (by means of the EuroQOL-questionnaire with five dimensions (EQ-5D*).

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.

In women who plan 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 the patient could develop anti-placental antibodies after receiving study drug. Such antibodies could interfere with the 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Has informed consent form (ICF) signed by patient or legal representatives or independent investigator, according to local rules and regulations.
2. Is aged 18 to 85 years, inclusive.
3. Is admitted to the ICU or intermediate care unit
4. Has diagnosis of sepsis (<96 hours prior to first study drug administration or <72 hour prior to AKI diagnosis)), according to criteria defined by the American College of Chest Physicians/Society of Critical Care Medicine (Bone 1992]), based on:
a. Has a proven or strongly suspected bacterial infection.
b. Has at least 2 of the following 4 SIRS criteria within the timeframe of 48 hours at time of screening and 72 hours prior to first study drug administration. Note: symptoms are not required to be present simultaneously at study randomization:
i. Has a core temperature > 38°C or < 36°C.
ii. Has a heart rate > 90 beats/minute (unless the patient has a medical condition known to increase heart rate or is receiving treatment to prevent tachycardia).
iii. Has a respiratory rate > 20 breaths/minute, $PaCO_2$ < 32 mm Hg or the use of mechanical ventilation for an acute respiratory process.

iv. Has a white cell count > 12 000/mm3 or < 4000/mm3 or a differential count showing > 10% immature neutrophils (band cells).
5. Has first diagnosis of AKI, defined as any of the following:
AKI Stage 1 or greater, according to the following Acute Kidney Injury Network (AKIN) criteria (Note: adjusted in regards to time-window):
a. Increase (absolute) in serum creatinine > 26.2 µmol/L (0.30 mg/dL) compared with a serum creatinine value within the previous 48 hours, or presumed to have occurred in the previous 48 hours when compared to a reference* creatinine value
b. Increase (relative) in serum creatinine to > 150% (> 1.5-fold) compared with a serum creatinine value in the previous 48 hours or presumed to have occurred in the previous 48 hours when compared to a reference creatinine value. The reference creatinine value is a serum creatinine value in the following order of preference:
i. Lowest value within 3 months of the hospital admission. If not available:
ii. At hospital admission. If not available:
iii. At ICU admission. If not available:
iv. Lowest value between 3 and 12 months prior to hospital admission
c. Urinary output < 0.5 mL/kg/h for > 6 hours following adequate fluid resuscitation when applicable, in the absence of underlying primary renal disease.
6. When the diagnosis of AKI was made according to one of the AKIN serum creatinine criteria (absolute or relative increase, see inclusion criteria 5a and 5b), continuing AKI needs to be confirmed by a confirmative serum creatinine measure (that is corrected for fluid administrations) defined as no decrease in serum creatinine >= 26.2 µmol/L (>=0.30 mg/dL). The result must be available prior to randomization, within 24 hours after the primary AKI diagnosis so that administration of the first study treatment can be started within 24 hours after the first AKI diagnosis.
7. When the AKI diagnosis was made according to the AKIN urine output criteria (urinary output < 0.5 mL/kg/h for > 6 hours, see inclusion criterion 5c), the oliguria or anuria should still meet the AKIN urine output criteria prior to randomization and study drug administration; administration of study treatment must be started within 24 hours after first AKI diagnosis.

Exclusion criteria

1. Woman of childbearing potential with a positive pregnancy test (blood or urine), pregnant, or breastfeeding.
2. Weighs more than 115 kg (253 lb).
3. Has life support limitations (e.g., do not intubate, do not dialyze, do not resuscitate).
4. Is known to be human immunodeficiency virus positive.
5. Has urosepsis.
6. Is already on dialysis (RRT) or or a decision has been made to initiate RRT within 24 hours

after planned start of study drug administration.
7. Is receiving immunosuppressant treatment or is on chronic high doses (high-dose therapy exceeding 2 weeks of treatment) of steroids equivalent to prednisone/prednisolone 0.5 mg/kg/day, including solid organ transplant patients. Patients with septic shock treated with hydrocortisone (e.g., 3 × 100 mg) can be included.
8. Is expected to have rapidly fatal outcome (within 24 hours).
9. Has known, confirmed fungal sepsis.
10. Has advanced chronic liver disease, confirmed by a Child-Pugh score of 10 to 15 (Class C).
11. Has acute pancreatitis with no established source of infection.
12. Has participated in another investigational study within 30 days prior to enrollment into the study.
13. Is not expected to survive for 28 days due to medical conditions other than SA-AKI, including cancer (previous hematological malignancies that are not actively treated allowable), end-stage cardiac disease, cardiac arrest requiring cardiopulmonary resuscitation or with pulseless electrical activity or asystole within the past 30 days, endstage lung disease, and end-stage liver disease.
14. Has known prior history of CKD with a documented estimated GFR (eGFR) < 60 mL/min by a commonly used formula such as Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), known GFR < 60 mL/min, or a known history of persistent creatinine level equal or greater than 150 µmol/L (1.70 mg/dL) prior to entry for reasons other than the current sepsis condition.
15. Has diagnosis of malaria or other parasite infections.
16. Has burns on > 20% of body surface.
17. Has had AKI diagnosis according to the AKI inclusion criteria for a period longer than 24 hours prior to study drug administration.
18. Is anticipated to be treated with non-continuous RRT from Day 1 to Day 7.
19. During Day 1 to Day 7 continuous RRT is anticipated to be started or stopped not according to per protocol criteria.
20. The AKI is most likely attributable to other causes than sepsis, such as nephrotoxic drugs (NSAIDs, contrast, aminoglycosides) and renal perfusion-related (acute abdominal aortic aneurysm, dissection, renal artery stenosis).
21. Improvement in serum creatinine of at least 0.30 mg/dL or (26.2 µmol/L) prior to administration of the study drug.
22. Patients who use nephrotoxic medication and who fulfill the SA-AKI inclusion criteria at screening are not eligible if the use of this nephrotoxic medication is planned to continue (e.g., NSAIDs, angiotensin-converting enzyme inhibitors, gentamycin, tobramycin). (Note: this is according to KDIGO Clinical Practice Guideline for AKI recommendations [KDIGO Acute Kidney Working Group 2012]) to avoid nephrotoxic medication).

23. Has a history of known IV drug abuse.
24. Is an employee or family member of the investigator or study site personnel.
25. Has active hematological malignancy

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-03-2015
Enrollment:	43
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Human Recombinant Alkaline Phosphatase
Generic name:	alkaline phosphatase

Ethics review

Approved WMO

Date:	19-08-2014
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-03-2016
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000761-40-NL
ClinicalTrials.gov	NCT02182440
CCMO	NL49271.091.14