1.0 TITLE PAGE

Study title:	A Phase-II, double-blind, randomized, placebo-controlled study on the safety and early efficacy of Alkaline Phosphatase in sepsis patients with renal failure.
Name of test drug/investigational product:	Alkaline Phosphatase
Study design:	Double-blind, randomized, placebo controlled, multicenter clinical trial (parallel group design (Final analysis)
Name of the sponsor:	AM-Pharma B.V. [redacted]
Protocol identification:	AP REN 01-01
EudraCT No.:	2007-003866-16
Development phase of study:	Phase II
Study initiation date:	First patient enrolled: 21 June 2008
Study completion date:	Last patient out: 30 November 2009 (Final analysis)
Name and affiliation of principal or coordinating investigator or sponsor's medical officer:	Professor J. G. van der Hoeven MD, PhD UMC Nijmegen University Medical Center St Radboud Department of Intensive Care [redacted]
Name of the company/sponsor signatory:	[redacted]
Date of report (Final):	07 May 2010

The study was conducted in compliance with Good Clinical Practice, Ethics Committee recommendations, informed consent regulations, the Declaration of Helsinki and with the laws and regulations of the country in which the study was conducted. Ethics approval of the *Protocol*, *Patient Information Sheet* and *Informed Consent Form* was received from local Ethics Committee before recruitment of the first patient.

2.0 SYNOPSIS

Name of sponsor: AM-Pharma BV	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use Only)**
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

Title of study:	A phase-II, double-blind, randomized, placebo-controlled study on the safety and early efficacy of alkaline phosphatase in sepsis patients with renal failure.	
Investigators:	Principal investigator: Professor JG van der Hoeven MD PhD. For other investigators, see Appendix 16.1.4.1	
Study centers:	(for Principal Investigator) UMC Nijmegen University Medical Centre St Radboud Department of Intensive Care [redacted] For other centers, see Appendix 16.1.4.1	
Publication (reference):	None, at the time of this report.	
EudraCT No:	2007-003866-16	
Study Period:	First Enrolment: 21 June 2008 Last Follow-up: 30 November 2009	**Phase of development:** Phase-II

Objectives:

This was an "exploratory therapeutic study" as defined in ICH E8 Harmonized Tripartite Guideline; General Considerations for Clinical Trials, whereby the objective is to "explore the use in the targeted indication" derived from a previous similar study "using surrogate or pharmacological endpoints and clinical measures" as per Guideline. In this regard, based on the results of a previous similar study, the objectives of the current study were:

- To investigate the effect of AP on renal function and associated clinical parameters in sepsis patients with renal failure.
- To investigate the safety and tolerability of AP in sepsis patients with renal failure.
- To investigate the pharmacokinetics of AP in sepsis patients with renal failure.
- To investigate the effect of AP on inflammatory parameters in sepsis patients with renal failure.

Methodology:

Randomized, double-blind, placebo-controlled, multicenter study. Medication was given in addition to standard care for sepsis patients with renal failure, with a 1/1 (AP/Placebo) randomization ratio. Patients were followed up for 28 days after the start of study drug administration.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

Number of patients:

Total Randomized: 36 (Placebo: 20; AP: 16). The Protocol planned to enroll a minimum of 26 patients with an APACHE-II score in the range 20-28, subject to an interim analysis at that point to adjust, if needed, the final sample size according to magnitude of treatment effect. Based on the results of the Interim Analysis, the Sponsor's Senior Management decided that no further recruitment would be needed and the trial was closed. At the point of trial closure 10 further patients had been enrolled, so all 36 patients enrolled are included in this report.

Diagnosis and Patient Selection:

Inclusion Criteria

- Patients aged 18-80 years, inclusive.
- Diagnosis: proven or suspected infection.
- Two out of four SIRS criteria of systemic inflammation, as follows:
    - Core temperature $\geq$38° or $\leq$36° Celsius.
    - Heart rate $\geq$90 beats/minute (unless the patient has a medical condition known to increase heart rate or is receiving treatment that would prevent tachycardia).
    - Respiratory rate $\geq$20 breaths/minute, $PaCO_2$ $\leq$32mmHg or the use of mechanical ventilation for an acute respiratory process.
    - White-cell count $\geq$12,000/mm^3 or $\leq$4,000/mm^3 or a differential count showing >10% immature neutrophils.
- Acute renal failure, defined as:
    - Rise in serum creatinine level to $\geq$150µmol/L (1.70mg/dL) within the previous 48 hours, in the absence of primary underlying renal disease, OR
    - Minimally at Stage 1 Kidney Injury according to AKIN creatinine criteria: Increase in serum creatinine $\geq$26.2µmol/L (0.30mg/dL) or increase to $\geq$150% ($\geq$1.5–fold) from baseline in the previous 48 hours in the absence of primary underlying renal disease and where baseline creatinine is less than 150µmol/L (1.70mg/dL)), OR
    - Minimally at Stage 1 Kidney Injury (AKIN) Urine Output criteria: Urine Output $\leq$0.5mL/kg/h for $\geq$6h and following adequate fluid resuscitation when applicable, in the absence of underlying primary renal disease and where baseline creatinine is less than 150µmol/L (1.70mg/dL).
- Written informed consent obtained prior to any study intervention.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

Diagnosis and Patient Selection (cont'd):

Exclusion Criteria

- Pregnant women or nursing mothers and fecund females who are not on effective contraception (chemical: pill; or mechanical: IUD).
- Known HIV (sero-positive) patients.
- Patients already on dialysis (RRT) at entry.
- Patients receiving immunosuppressant therapy or on chronic high doses of steroids equivalent to prednisone 1mg/kg/day.
- Patients expected to have rapidly fatal disease within 24 hours.
- Known confirmed gram-positive sepsis.
- Known confirmed fungal sepsis.
- Acute pancreatitis with no established source of infection.
- Any previous administration of active study medication.
- Participation in another investigational study within 90 days prior to start of the study which might interfere with this study.
- Patients not expected to survive for 28 days due to other medical conditions such as end-stage neoplasm or other diseases.
- Known allergy to dairy (bovine) products including cow milk.
- Sepsis without renal failure as defined in the Entry Criteria.
- History of chronic renal failure or history of persistent creatinine level equal or greater than 150µmol/L (equivalent to 1.70mg/dL) prior to entry for reasons other than the current sepsis condition.

Test product, Dose, Mode of Administration, Batch Number:

AP was administered intravenously (IV) as an initial bolus injection of 67.5U/kg over 10min, followed by a continuous infusion of 132.5U/kg for 48h. [redacted] Expiry date: 01 January 2010.

Duration of treatment:

48 hours.

Reference therapy, dose and mode of administration, batch number:

Matching Placebo was administered intravenously, with volume and duration matching Active treatment. [redacted] Expiry date: 01 January 2010.

Criteria for evaluation:

Efficacy:

The Full Analysis Set (FAS) consisted of all randomized subjects who received any study medication and had at least one post-baseline value.

The Intention-to-treat population (ITT) consisted of all randomized subjects who received any study medication for longer than one hour.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

The per protocol population (PP) consisted of all randomized patients who fulfilled the entry/exclusion criteria, and completed the protocol as planned.

Safety:

The safety population (SAF) consisted of all subjects who received any study medication in any of the two treatment groups.

An independent Drug Safety Monitoring Board (DSMB; per ICH Guidelines) was responsible for reviewing all safety aspects of the study, AEs and SAEs including deaths. The independent DSMB was based in the United Kingdom and was composed of:

Statistical Methods:

According to Statistical Analysis Plan dated 22.01.2010, prior to final unblinding.

The efficacy analysis consisted of descriptive statistics including means, SD, minima, maxima, lower quartiles, medians, upper quartiles and number of observations for quantitative variables; and frequencies and percentages (frequency distribution) for categorical variables. Mean treatment differences were calculated with corresponding 95% confidence intervals for the primary endpoints (per timepoint and absolute changes from BL). ANCOVA with BL value of the variable as covariate was used for primary endpoints. Time–to-event-data were analyzed by means of log-rank tests and Kaplan-Meier estimates. Sensitivity analyses including regression analysis were calculated.

As an overall measure p-value (one-sided) of the primary endpoints was combined according to the method of Hartung.

The safety analysis consisted of dichotomous (yes/no) outcomes from safety variables, compared between treatment groups by Fisher's exact test.

Pharmacokinetics:

There were no formal PK evaluations. However, serum enzyme activity was evaluated to ascertain whether the values were broadly similar to those of previously reported trials.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

Results:

Analysis Groups

- Safety Population (SAF): all randomized patients who received any study medication.
- Intention-to-treat Population (ITT): all randomized patients who received any study medication for longer than 1 hour.
- Full Analysis Set Population (FAS): all randomized patients who received any study medication and had at least one post-baseline value.
- Per-protocol Population (PP): all randomized patients who fulfilled the entry/exclusion criteria and completed the protocol as planned.

Populations Analyzed

	AP (n)	Placebo (n)	Total (n)
SAF	16	20	36
ITT	16	19	35
FAS	15	19	34
PP	14	18	32

Comparability Between Groups at Entry

Demographics and disease severity parameters at baseline were comparable and very similar for the two treatment groups. One subject (Placebo) was excluded from most efficacy analyses due to not having any post-baseline data (early death), but was included in the safety analysis.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

Baseline Comparability Between Groups (ITT)

BASELINE PARAMETER	AP (n=16)	Placebo (n=19)
Male: n (%)	13 (81)	14 (74)
Age: mean years (SD)	65 (12)	67 (15)
Height: mean cm (SD)	176 (10)	174 (8)
Weight: mean kg (SD)	86 (12)	80 (14)
Heart rate: mean bpm (SD)	103 (23)	105 (22)
Systolic BP: mean mmHg (SD)	103 (26)	110 (26)
Diastolic BP: mean mmHg (SD)	52 (13)	55 (13)
Temperature: mean °C (SD)	37 (1)	37 (1)
APACHE-II score: mean (SD)	24 (7)	23 (8)
SOFA score: mean (SD)	10 (4)	11 (5)
Serum creatinine: median µmol/L (IQR)	172 (126;198)	173 (115;268)
Creatinine clearance: mean mL/min (SD)*	50 (27)	40 (37)

Notes: all patients were Caucasians. *: missing values estimated by Cockroft-Gault formula.

Primary Efficacy Variables:

The results for the prospectively sought primary efficacy variables related to renal function parameters, namely (a) renal replacement therapy (RRT) requirement; (b) creatinine clearance; and (c) serum creatinine level.

RENAL REPLACEMENT THERAPY (RRT) REQUIREMENT:

According to the Protocol criteria for RRT intervention requirement (per ADQII Consensus) the results were favorable to the AP group relative to Placebo in all 3 measurements of RRT intervention, namely (a) for all patients, RRT intervention as Yes/No for any intervention throughout the 28-day study period; (b) for all patients[1], total duration (mean hours on RRT); and (c) for patients requiring RRT, relative duration (percentage time on RRT relative to total time from entry to end of follow-up or death). All RRT interventions were continuous veno-venous hemofiltration (CVVH), which was associated with stable (lower) serum creatinine values throughout the intervention period.

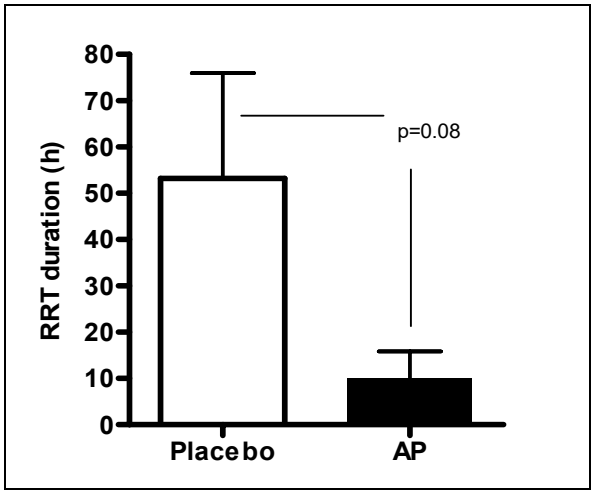
Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

Renal Replacement Therapy Requirement (ITT)

	AP (n=16)	Placebo (n=19)
RRT required: n	3 (19%)	7 (37%)
RRT not required: n	13 (81%)	12 (63%)
p*	0.2853	
Mean duration of RRT: hours (SD)	10 (23)	53 (99)
p**	0.0801	
Relative RRT Duration* (patients requiring RRT): % (SD)**	12 (4.8)	34 (15.8)
p**	0.0456	

*: Fisher's exact test; **: T-test, ***:[(Cumulative RRT duration)/(Time (d) in the study)]*100%

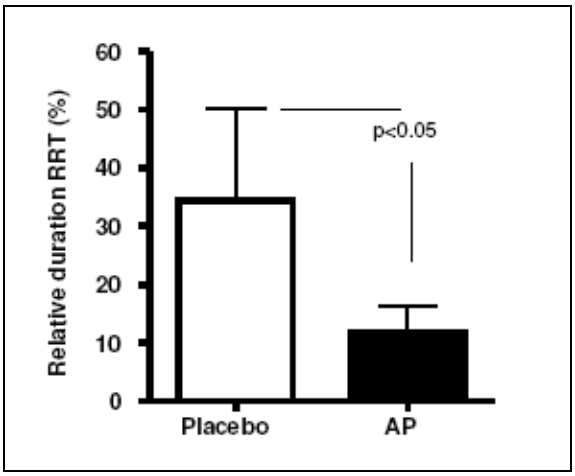
Duration of RRT (ITT; means/SEM)



p: t-test

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

Relative Duration of RRT (ITT; means/SEM)

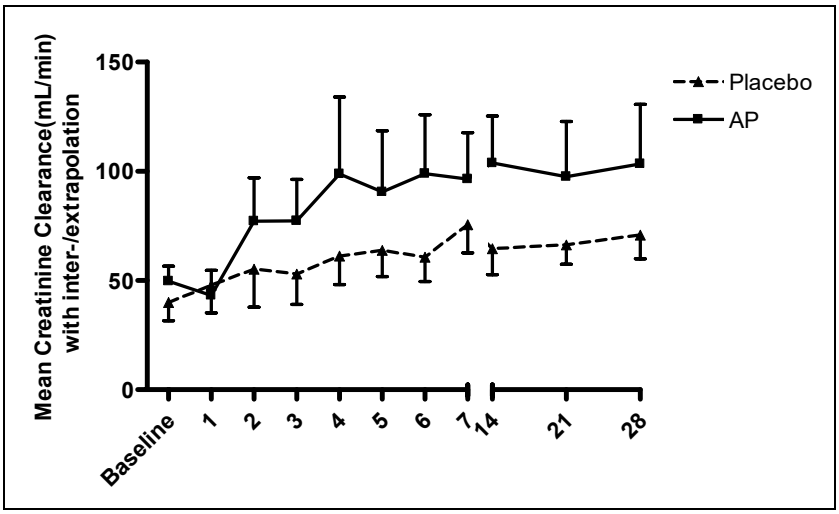


p: t-test; (cumulative RRT duration)/(time (d) in the study)/*100%

CREATININE CLEARANCE:

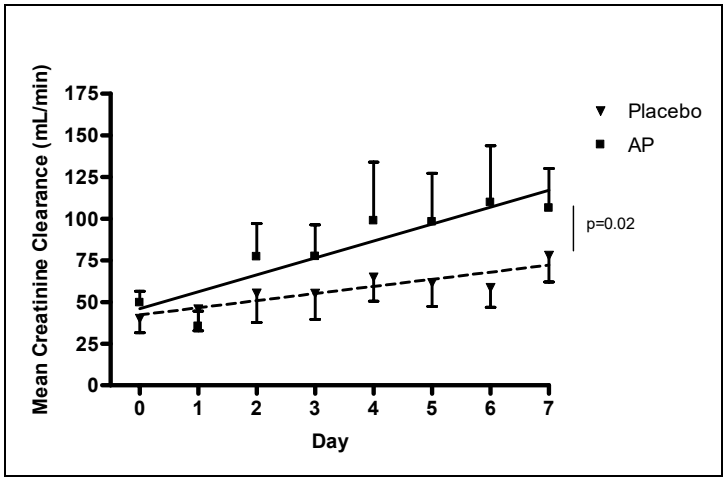
The results of creatinine clearance data confirmed that the AP group was superior to Placebo, both during the first 7 days and throughout the 28-day period. There was a clear separation of observed values between groups starting on Day 2 after treatment. Over the 28-day period, creatinine clearance was significantly superior for the AP-treated group relative to Placebo (p=0.0148; repeated measures ANOVA).

Progression of Creatinine Clearance Adjusted for Missing Values (FAS; means/SEM)



Analysis of creatinine clearance values (regression) corrected for baseline also confirmed a significant (p=0.0181) and progressive effect of AP on clearance levels from baseline to Day 7, relative to Placebo.

Creatinine Clearance 0-7 Days (FAS; means/SEM)



SERUM CREATININE:

Since serum creatinine levels are greatly affected by RRT intervention, they do not reflect renal function when RRT is present, and there is no possibility of correcting values to adjust for this effect. As the results of this study showed a higher number of patients on RRT in one of the groups (two-fold higher on Placebo), the effects of AP relative to Placebo on serum creatinine levels cannot be interpreted, except that the observed levels on Placebo (n=7/19 on RRT) are a substantial underestimation relative to the AP group (n=3/16 on RRT). Despite the impossibility of correcting values for RRT-effect on serum creatinine, the AP group had consistently lower values, both for the periods 0-7 and 0-28 days.

AUC Serum Creatinine (μmol/L; FAS)

	AP	Placebo	Q1; Q3	
			AP	Placebo
Mean (SD) 0-7 days	1100 (510)	1411 (844)	726; 1265	711; 1978
Mean (SD) 0-28 days	4092(2623)	4285 (2920)	2298; 4834	2401; 4563

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

OVERALL EFFECTS ON RENAL PARAMETERS:

Analysis of all main efficacy variables (to evaluate overall treatment effect on renal function per Statistical Plan) confirmed that all appropriate combinations tested were significant for AP treatment benefit.

Analysis of Combined Renal Function Variables (ITT)

Legend:
A: RRT requirement (0-28d)
B: RRT cumulative duration (0-28d), including all patients
C: RRT relative duration (0-28d)
D: Creatinine Clearance linear regression (0-7d)
E: AUC Serum creatinine without RRT correction (0–7d; day 0 as covariate)

Combined Parameters	p-value*
A+C+D+E	0.005
B+D+E	0.001
A+C+D	0.018
B+D	0.016

*: one-sided.

Secondary Efficacy Variables:

The results for the prospectively sought secondary efficacy variables related to (a) length of hospital/ICU stay; (b) SOFA Score; (c) length of mechanical ventilation; and (d) all-cause mortality.

LENGTH OF ICU/HOSPITAL STAY:

Since deaths may bias length of stay, this parameter was analyzed without deaths during the study period (subgroup A) and including deaths (subgroup B).

Mean stay at ICU was significantly shorter by >2-fold for the AP group in subgroup A (p=0.0174), while subgroup B showed a trend in favor of the AP group (p=0.1099). Total length of hospital stay also showed longer stay for Placebo, by 42% relative to the AP group in subgroup A, although the difference did not reach significance. The results showed that shorter overall hospitalization was not achieved at the expense of longer ICU stay.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

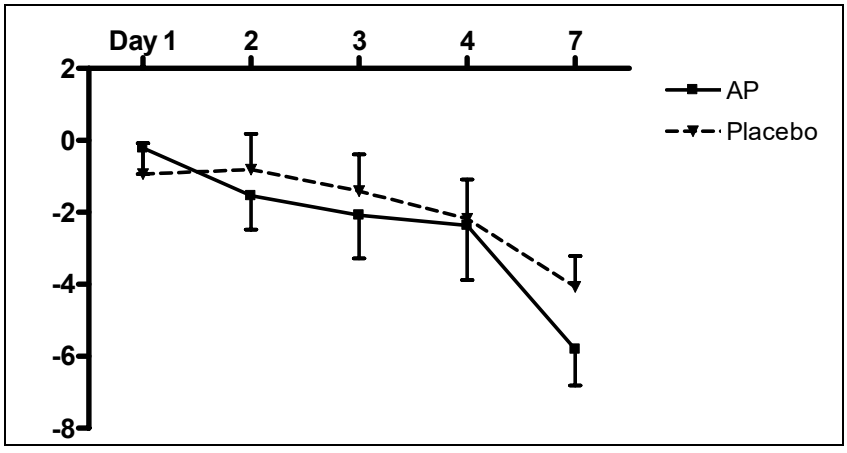
Length of Stay in ICU and Hospital (ITT)

	AP	Placebo
Subgroup A		
ICU Stay (days): mean (SD)	10.9 (7.5)	24.5 (17.9)
AP-Placebo (95% CI)	13.6 (-24.5; -2.6)	
p*	0.0174	
Hospital Stay (days): mean (SD)	30.7 (26.4)	47.1 (35.7)
AP-Placebo (95% CI)	-16.4 (-43.8; 10.9)	
p*	0.2261	
Subgroup B		
ICU Stay (days): mean (SD)	13.9 (9.8)	23.6 (17.6)
AP-Placebo (95% CI)	-9.7 (-21.8; 2.4)	
p*	0.1099	

SOFA SCORE:

Overall progression of severity, related to organ failure as evaluated by the SOFA score of six main organ systems showed greatest improvement, as expected, in the 7 days after entry in both treatment groups. Progression from similar baseline scores, the improvement was 30% greater on AP relative to Placebo, but did not reach statistical significance.

Changes in SOFA Score (ITT; means/SEM)

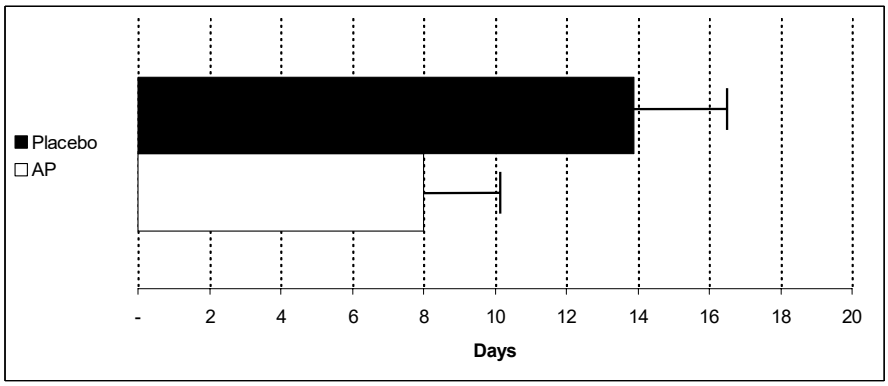


Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

LENGTH OF MECHANICAL VENTILATION:

At entry, 13/16 patients on AP and 13/20 patients on Placebo were on mechanical ventilation in the Safety population. Thereafter, up to Day 28 one further patient on AP and 3 further patients on Placebo required mechanical ventilation. Duration of mechanical ventilation showed a trend in favor of the AP group (t-test: p=0.0938, ITT), with mean (SEM) duration of 8.0 (2.1) days for the AP group and 13.9 (2.6) days for the Placebo group.

Length of Mechanical Ventilation (ITT; means/SEM)



ALL-CAUSE MORTALITY:

At Day 28 all-cause-mortality was relatively low (n=12; 33%) with no significant differences between treatment groups (Log-rank: p=0.2532). Overall, there were seven deaths on AP and five on Placebo. The causes of deaths were attributed to the underlying condition in all cases. One further death was recorded during the study, but it was excluded from mortality calculations for having occurred outside the follow-up period (at Day 40; Placebo group). As per Protocol, all death reports (narratives) were reviewed individually by the independent DSMB.

Safety:

All safety data were reviewed by the independent DSMC and did not raise a safety concern. The incidence and type of adverse events (AEs) were as expected for a population with sepsis and renal failure. At the point of final database lock, the overall event incidence was similar in the two treatment groups (AP: 94%; Placebo: 100%). Serious adverse events reflected the severity of disease. The DSMB reported that AP had a favorable safety profile in the seriously ill patients enrolled in the trial and has a potentially positive risk/benefit ratio in these patients. Measurements of antibodies (total Ig, IgG-anti-BIAP, IgE) up to Day 28 did not raise clinical reports or other evidence of major antigenicity during the study period.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

Summary of AEs (SAF)

		AP	Placebo
ALL AEs	n (%)	130 (100)	154 (100)
Treatment-emergent AEs	n (%)	124 (95)	147 (96)
Patients with Treatment-emergent AEs	n (%)	15 (94)	20 (100)
Non-serious Treatment-emergent AEs*:			
Atrial fibrillation	n	3	6
Diarrhea		6	3
Hypotension		2	7
Delirium		2	5
Decubitus ulcer		1	4
Abdominal pain		3	2
Pyrexia		1	4
Impaired gastric emptying		3	2
Tracheostomy		1	3
Constipation		1	3
Restlessness		2	2
Atrial flutter		1	3
Tachycardia		.	3
Hypertension		2	1
Edema peripheral		2	1
Pneumothorax		.	3
Pain		1	2
Confusional state		1	2
Hypokalemia		3	.
Agitation		1	2
Insomnia		1	2
Hemoglobin decreased		2	1
Oxygen saturation decreased		3	.

*: includes >2 events reported in either treatment group

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

Summary of SAEs (SAF)

		AP	Placebo
All Serious Treatment-emergent AEs			
Septic shock	n	2	2
Respiratory failure		3	1
Gastrointestinal necrosis		2	.
Hypotension		.	2
Death		2	.
Hepatic necrosis		1	.
Gallbladder necrosis		1	.
Electrolyte imbalance		1	.
Azotemia		1	.
Cardiac arrest		.	1
Bradycardia		.	1
Electrocardiogram QT prolonged		.	1
Blood calcium decreased		.	1
Coma		.	1
Hyperlactacidemia		.	1
Depressed level of consciousness		.	1
Osteomyelitis		1	.
Brain neoplasm		.	1
Renal failure		.	1
Therapy cessation		1	.
Echocardiogram abnormal		1	.

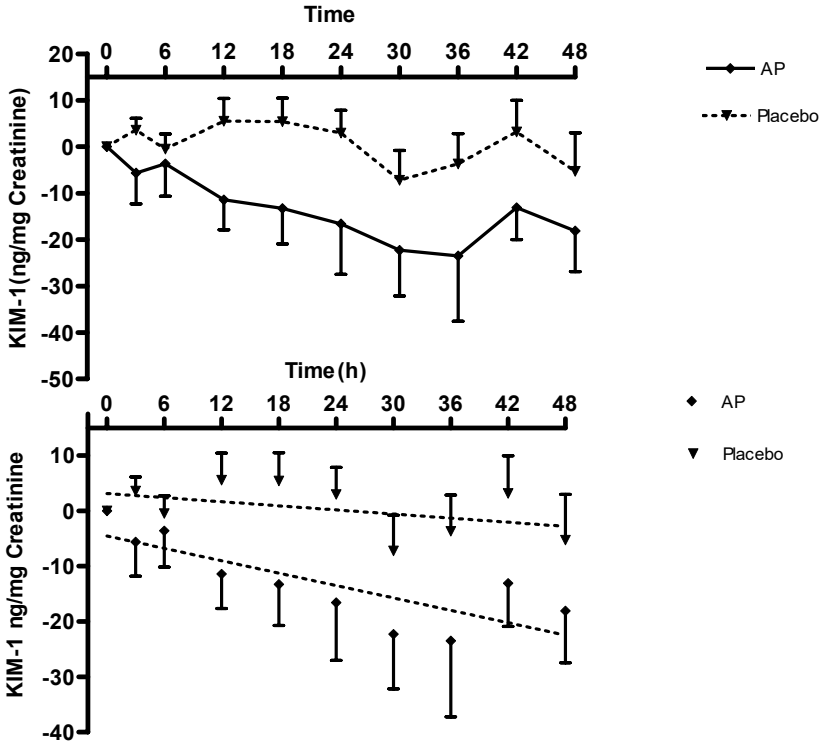
Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

Markers of Renal Tissue Damage and Inflammation

Regarding evaluations of markers of renal injury, KIM-1 and IL-18 showed significant improvements in favour of AP-treated patients during the treatment period, while the other markers (NGAL, GST-alpha, GST-pi, IL-6) did not show differences between treatment groups. Regarding the soluble acute-phase protein LBP, there was significant difference improvement in the AP-treated relative to placebo.

KIM-1: The figure below displays the results of KIM-1 evaluations in the period 0-48h as progress curves and as trends.

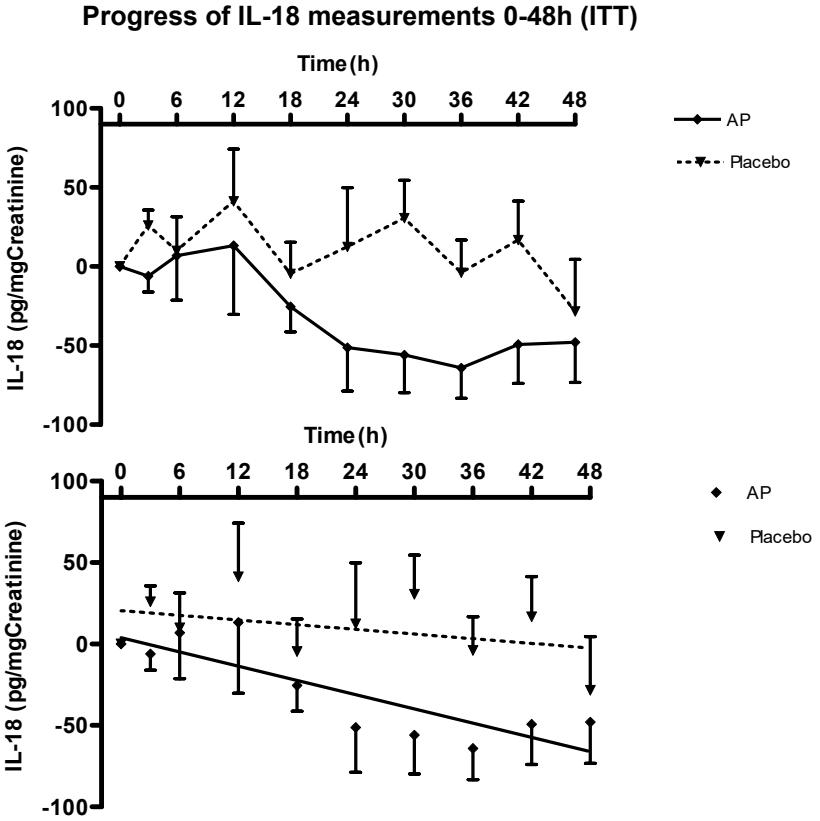
Progress of KIM-1 measurements 0-48h (ITT)



With regard to KIM-1 measurements, the above results showed a statistically significant difference (paired t-test; p= 0.0002) between groups in favour of AP treatment during the treatment period.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

IL-18: The figure below display the results of IL-18 evaluations in the period 0-48h as progression curve and as trend.

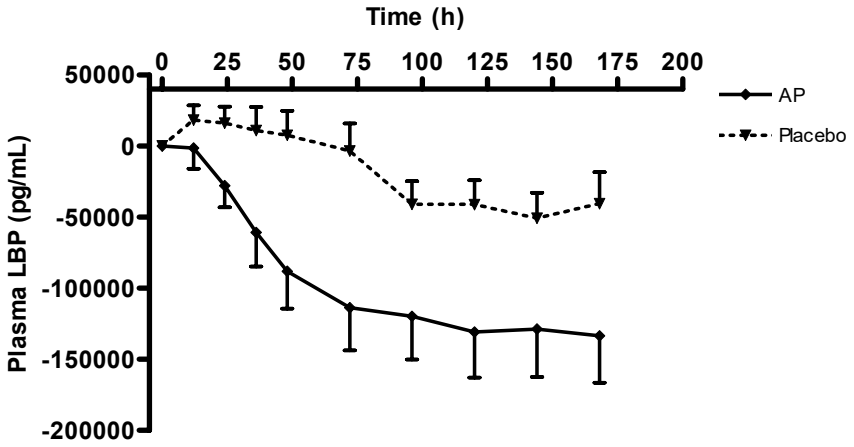


With regard to IL-18 measurements, the above results showed a statistically significant difference (paired t-test; p=0.0027) between groups in favour of AP treatment during the treatment period.

Name of sponsor: AM-Pharma BV	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use Only)**
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

LBP: The figure below displays the results for the soluble acute-phase LBP evaluations in the period 0-7 days.

Progress of soluble acute-phase LBP measurements 0-7d (ITT)



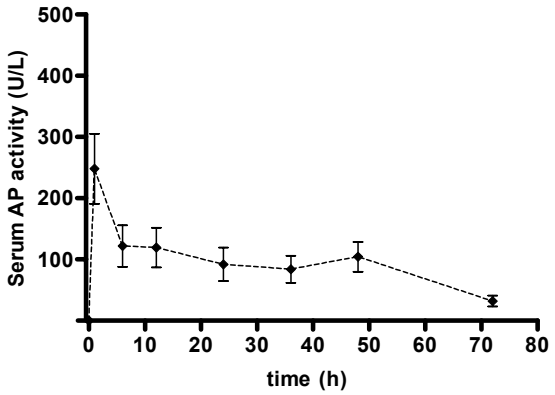
With regard to LBP measurements, the above results show a statistically significant difference (paired t-test; p=0.0002) between groups in favour of AP treatment up to Day 7.

Name of sponsor: AM-Pharma BV	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use Only)
Name of finished product: AP	Volume:	
Name of active ingredient:	Page:	

Pharmacokinetics:

The AP serum activity levels evaluations showed results that were very similar to those observed in previous trials. AUC estimations were not planned and were not calculated because the sampling times do not allow appropriate evaluation of either absorption after the initial bolus or the elimination curve. Likewise, the restricted samplings do not allow appropriate estimation of $T_{½}$ and T_{max} although the observed C_{max} values were within 1h of starting medication.A summary of the AP serum activity evaluations from the 13 patients analysed is displayed below.

AP Serum Activity Levels (n=13; means/SEM)



AP Serum AP Activity (n=13)

Sampling Time (h)	1	6	12	24	36	48	72
Mean activity (U/L)	247.95	121.85	119.40	91.95	83.98	104.22	32.05
SD	206.51	116.69	117.11	94.63	76.76	76.75	29.77
Median (U/L)	137.78	58.89	56.30	50.19	51.49	85.00	27.41
Q1 (U/L)	110.74	50.83	42.59	31.85	31.20	51.02	14.08
Q3 (U/L	327.26	176.67	190.13	91.94	88.52	121.30	36.21

C_{max} mean (U/L)	277.51
SD	211.36
C_{max} median (U/L)	210.74

Name of sponsor: AM-Pharma BV	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use Only)**
Name of finished product: AP	**Volume:**	
Name of active ingredient:	**Page:**	

Conclusions:

For the main efficacy variables, the results of study AP REN 01-01 demonstrated that all the key parameters of renal function are improved significantly on active treatment relative to placebo, namely requirement for RRT, creatinine clearance and serum creatinine. The treatment effects on serum creatinine are more discrete than the other renal parameters due to strong RRT interference on creatinine levels.

For the secondary efficacy variables, the key parameters of clinical progression (length of ICU and hospital stay, length of mechanical ventilation, SOFA score) all corroborate the findings in the primary variables on renal function, while all-cause mortality was not affected. Regarding evaluations of markers of renal injury, KIM-1 and IL-18 showed significant improvements in favour of AP-treated patients during the treatment period, while the other markers did not show differences between treatment groups. Likewise, evaluation of soluble acute-phase LBP showed a significant improvement for the AP-treated group up to Day 7, relative to placebo. The improvements in secondary variables suggest that the observed renal function effects following AP-treatment are reflected in overall faster recovery of patients.

Regarding safety, the results of study AP REN 01-01 confirmed that AP treatment is well-tolerated by patients with sepsis and renal failure, with reported events being mostly related to the progression and/or complications of the underlying disease(s).

Report Date: 07 May 2010