Clinical Study Report Synopsis

Exploratory efficacy and safety, pharmacokinetics and dosefinding study of ATryn® (antithrombin alfa) in patients with disseminated intravascular coagulation associated with severe sepsis

A phase II study with 5 days IV infusion of ATryn®, a freeze dried powder for solution for infusion

An international, multi-centre, centrally randomised, controlled, open label with blind adjudication, dose escalation study in 3 steps

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Clinical Development

LEO 90010-I21
Report Date 18-DEC-2009
EudraCT number: 2006-002873-35

1 CLINICAL STUDY REPORT SYNOPSIS APPROVAL

1.1 APPROVAL STATEMENT

On behalf of LEO, only the Vice President, International Clinical Development, LEO and the Head of Biostatistics, LEO HQ are authorised to approve the Clinical Study Report Synopsis.

All LEO approvers will be identified on a signature page of the pdf-file of the final Clinical Study Report Synopsis when the last LEO approval is obtained. The time and date of their e-signatures are likewise presented on the approval page.

The following persons have approved this Clinical Study Report Synopsis using electronic signatures:

[redacted] _____
[redacted] Biostatistics, LEO HQ

[redacted] _____
[redacted], International Clinical Development, LEO

1.2 APPROVAL STATEMENT INVESTIGATORS

On behalf of all investigators, the International Co-ordinating Investigator approves the Clinical Study Report Synopsis. The International Co-ordinating Investigator approves the Clinical Study Report Synopsis by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this document.

The following person has approved this Clinical Study Report Synopsis

[redacted] _____
International Co-ordinating Investigator

2 SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: ATryn®	Volume:	
Name of Active Substance: (recombinant) antithrombin alfa	Page:	

Title of study:

LEO 90010-I21. Exploratory efficacy and safety, pharmacokinetics and dosefinding study of ATryn® (antithrombin alfa) in patients with disseminated intravascular coagulation associated with severe sepsis

International Co-ordinating Investigator:

[redacted], United Kingdom,

tel: [redacted], fax: [redacted], e-mail: [redacted]

Centre details:

The total number of recruiting sites were 14 (France: 11, Germany: 1, United Kingdom: 2)

Publication (reference):

Not applicable

Studied period:	Phase of development:
First enrolment 03-AUG-2007, Last patient completed 02-DEC-2008	II

Objectives:

The Primary objective was to explore the efficacy and safety of ATryn® for the treatment of DIC associated with severe sepsis, when administered by continuous intravenous (IV) infusion over five days. The secondary objectives were to obtain pharmacokinetic data in patients with DIC associated with severe sepsis and to establish an appropriate dose regimen for phase III studies.

Methodology:

An international, multi-centre, centrally randomised, controlled, open label with blind adjudication, dose escalation study in 3 steps. No stratification was made.

Number of subjects enrolled:

It was decided to discontinue the study prematurely due to extremely low recruitment rate. Only 25 of the originally 200 intended patients were enrolled. Ten patients in group AT 150, 10 patients in group AT 250 and 5 patients in the control group.

Diagnosis and main criteria for eligibility:

Diagnosis: Severe sepsis with disseminated intravascular coagulation.

Main inclusion criteria according to study protocol version 3 dated 05-MAY-2008

1. Signed informed consent has been obtained from the patient or his/her legally acceptable representative
2. Severe sepsis defined as:

a. Systemic inflammatory response syndrome (SIRS) related to the current sepsis episode with at least three of the following clinical findings:

- body temperature (rectal, ear or core) > 38°C or < 36°C;
- heart rate > 90 beats/minute;
- hyperventilation (evidenced by a respiratory rate of > 20 breaths/minute or a PaCO2 of < 32 mmHg) or mechanical ventilation;
- leucocyte count > $12x10^3$ cells/µl or < $4x10^3$ cells/µl

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: ATryn®	Volume:	
Name of Active Substance: (recombinant) antithrombin alfa	Page:	

(if a medical condition or medication prevents tachycardia, two SIRS criteria was acceptable)

and

b. Minimum one sustained organ failure (respiratory failure, renal dysfunction, hepatic dysfunction, metabolic acidosis or septic shock).

Presence of DIC is considered second organ failure.

and

c. Clinical signs of infection caused by a bacterial or fungal pathogen

3. Disseminated intravascular coagulation (≥ 5 points on overt or non overt DIC score)
4. Maximum time from diagnosis of first organ failure to randomisation: 48 hours.

   Maximum time from diagnosis of DIC to randomisation: 24 hours.
5. At least 18 years of age
6. Males or non-pregnant females. Females of child bearing potential should have a negative urine or serum pregnancy test within 24 hours prior to drug administration
7. Any ethnic origin
8. Patient hospitalised at an intensive care unit (ICU)
9. At the time of enrolment there has to be intent by physicians and families to aggressively treat the patient

Main exclusion criteria according to study protocol version 3 dated 05-MAY-2008

1. Previous treatment with an antithrombin concentrate or recombinant human activated protein C (rhAPC) within the current sepsis episode
2. Treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at any dose within the last 6 or 18 hours before randomisation, respectively
3. Anticipated need for treatment with UFH/LMWH, pentasaccharide (e.g. fondaparinux), oral anticoagulants or thrombolytic agents during 6 days post randomisation (e.g. current VTE, atrial fibrillation, ongoing VTE prophylaxis or hypercoagulable state)
4. Intended treatment with rhAPC during 6 days post randomisation
5. Treatment with oral anticoagulants within the last 48 hours before randomisation and INR above 1.5
6. Treatment with: clopidogrel, glycoprotein IIb/IIIa inhibitors or acetylsalicylic acid at doses >325 mg/day within 5 days prior to randomisation.
7. Anticoagulant treatment with pentasaccharide (e.g. fondaparinux) within 7 days prior to randomisation
8. Conditions other than sepsis anticipated to be terminal within 6 months
9. Known bleeding disorder other than DIC
10. Chronic vegetative state
11. Incurable malignancy with documented metastases
12. Haematological neoplasia where cytostatic treatment has been administered within two months prior to randomisation
13. Bone marrow aplasia or treatment induced low platelet count (due to immunosuppressive medication)
14. Preexisting dialysis-dependent renal failure
15. Known advanced chronic liver disease corresponding to Child-Pugh class C (measured prior to ICU admission outside the current sepsis episode) or any history of bleeding from oesophageal varices
16. Overt, ongoing serious haemorrhage

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: ATryn®	Volume:	
Name of Active Substance: (recombinant) antithrombin alfa	Page:	

17. Advanced directive to withhold life-supporting treatment (except cardiopulmonary resuscitation)
18. Major burns involving >20% of the body surface
19. Platelet count <$20x10^3$/µl (patients should not be included if they require a platelet transfusion to bring their platelet level above $20x10^3$/µl just prior to randomisation)
20. Acute Myocardial Infarction within 7 days prior to randomisation
21. Recent (within 30 days prior to randomisation) or planned (during 6 days post randomisation) heart surgery with cardio-pulmonary bypass
22. Transplantation within 30 days prior to randomisation
23. History of stroke within the last 90 days prior to randomisation
24. Severe cranial or spinal trauma within the last 90 days before randomisation or known cranial or spinal space occupying lesion, intracerebral arteriovenous malformation or cerebral aneurysm
25. Epidural catheter within 12 hours before randomisation or planned epidural catheter during 6 days post randomisation
26. Recent (within 30 days prior to randomisation) or planned (during 6 days post randomisation) cranial or spinal surgery (except nontraumatic lumbar puncture)
27. Any major surgery with increased high risk of bleeding within 12 hours before randomisation or planned major surgery with increased high risk of bleeding during 6 days post randomisation (except tracheostomy)
28. Trauma patients with increased risk of bleeding e.g. significant contusion to lung, liver or spleen, retroperitoneal bleed, pelvic fracture or compartment syndrome within 48 hour before randomisation
29. Known or suspected hypersensitivity to component(s) of investigational products or known or suspected hypersensitivity to goats or goat products
30. Current participation in any other interventional clinical trial
31. Patients who have received treatment with any non-marketed drug substance (i.e., an agent which has not yet been made available for clinical use following registration) within the last 30 days prior to randomisation
32. Previously enrolled in any trial of ATryn®

Investigational product, dose, method of administration, lot numbers:

ATryn® (recombinant antithrombin alfa) freeze dried powder for solution for intravenous infusion. ATryn® was given as a bolus followed by continuous intravenous infusion for 5 days in a dosage aimed to obtain a plasma level of 150% and 250% antithrombin activity in the dosage groups of AT-150 and AT-250 respectively. Lot numbers (Manufacturers lot no./Customers lot no.): (5028.1/06C03-6), (5028.2/06C10-6), (5028.4/06D14-6), (5028.6/06K13-6), (5028.7/06C03-6), (5028.8/06L17-6), (5028.10/06M08-6)

Reference product, dose, method of administration, lot numbers:

No reference product used. Control patients received standard treatment.

Duration of treatment:

Continuous i.v. infusion for 5 consecutive days.

Criteria for evaluation：

Primary efficacy criterion: Patients alive on day 28, having had an improvement in the DIC score (overt or non-overt) by at least 2 points between baseline and day 6 and having had no worsening of the Sepsis-related Organ Failure Assessment (SOFA) score between baseline and day 6

Secondary efficacy criteria:

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: ATryn®	Volume:	
Name of Active Substance: (recombinant) antithrombin alfa	Page:	

- 28 days and 90 days mortality
- Change from baseline to day 6 in SOFA score among survivors on day 6
- Change from baseline to day 6 in DIC score among survivors on day 6
- Days alive and out of ICU day 28
- Days alive and out of hospital day 28
- Days alive and free of inotrope/vasopressor support day 28
- Days alive and off ventilator day 28
- Days alive and free of need for Renal Replacement Therapy day 28
- Change from baseline to day 6 in inflammation marker IL-6
- Change from baseline to day 6 in inflammation marker procalcitonin
- Pharmacokinetic (PK) parameters

Safety:

- Critical events (major bleedings, thromboembolic complications and deaths)
- Hypotension or intervention with vasopressors and/or inotropes in order to maintain blood pressure during the first 6 hours after start of ATryn® infusion
- All other adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), serious ad-verse drug reactions (SADRs)
- Immunological test results (antibodies against antithrombin alfa or goat milk proteins)

Statistical methodology

Due to the early termination of the trial with only 25 of 200 patients enrolled the planned Cochran-Mantel-Haenszel test for the primary efficacy criterion and the Fisher's exact test for the two first secondary efficacy criteria was not relevant to apply. Only descriptive statistics are presented.

Summary – Conclusions

Efficacy results:

Outcome primary efficacy criteria:

Patients alive on day 28, having had an improvement in the DIC Score (overt or non-overt) by at least 2 points between baseline and day 6 and having had no worsening of the SOFA score between baseline and day 6 was 2(20%), 2(20%), 2(40%) in the 150-AT, 250-AT and control group respectively.

Outcome secondary efficacy criteria:

The 28 days mortality was 1(10%), 4(40%) and 0(0%) in the 150-AT, 250-AT and control group respectively.

The 90 days mortality was 4(40%), 6(60%) and 0(0%) in the 150-AT, 250-AT and control group respectively

The mean change in SOFA score was -2.3, -5.5 and -3.0 in the 150-AT, 250-AT and control group respectively.

The mean change from baseline to day 6 in DIC score among survivors on day 6 was -3.0(1.7), -2.2(2.4) and -3.0(1.6) score (SD) in the 150-AT, 250-AT and control group respectively.

The mean number of days alive and out of ICU on day 28 was 9.8(10.8), 4.7 (10.0) and 13.6(8.4) days (SD) in the 150-AT, 250-AT and control group respectively.

The mean number of days alive and out of hospital on day 28 was 3.0(6.4), 3.0(6.6) and 4.6(7.4) days (SD) in the 150-AT, 250-AT and control group respectively.

The mean number of days alive and free of inotrope/vasopressor support on day 28 was 20.7(9.0), 12.4(11.7) and 21.6(6.8) days (SD) in the 150-AT, 250-AT and control group respectively.

The mean number of days alive and off ventilator on day 28 was 11.4 (10.5), 8.9 (11.8) and

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: ATryn®	Volume:	
Name of Active Substance: (recombinant) antithrombin alfa	Page:	

14.4(8.8) days (SD) in the 150-AT, 250-AT and control group respectively.

The mean number of days alive and free of need for renal replacement therapy day 28 was 22.6(13.3), 10.5(13.4) and 23.0(6.9) days (SD) in the 150-AT, 250-AT and control group respectively.
The mean change from baseline to day 6 in inflammation marker IL-6 was -68,429 (192,828), -131,53(31,801) and -69,651(141,889) pg/mL(SD) in the 150-AT, 250-AT and control group respectively.
The mean change from baseline to day 6 in inflammation marker procalcitonin was -203.8(340.2), -51.1(49.6) and -139.6(146.2) ng/mL(SD) in the 150-AT, 250-AT and control group respectively

Safety results:

Critical events included major bleedings, thromboembolic complications and deaths. The investigators reported 52 critical events until Day 28. The adjudication committee evaluated 35 of these events as critical. Additional 5 critical events were reported from Day 28 to Day 90 giving a total of 57 critical events reported during the study.
The total number of reported and adjudicated events (in brackets) until Day 28 are given below.

Critical events Group 150-AT

Until Day 28, ten (6) critical events were reported from this group: 1(1) death, 7(3) bleedings in 5(3) patients and 2(2) thromboembolic complications in 2(2) patients.

Critical events Group 250-AT

Until Day 28, twenty-eight (18) critical events were reported from this group: 4(4) deaths, 22(12) bleedings in 8(3) patients and 2(2) thromboembolic complications in 2(2) patients.

Critical events Control Group

Until Day 28, fourteen (11) critical events were reported from this group: no deaths, 12(9) bleedings in 4(4) patients and 2(2) thromboembolic complications in 1(1) patient.

Hypotension or intervention with vasopressors and/or inotropes in order to maintain blood pressure during the first 6 hours after start of ATryn® infusion. Data is available for 19 patients and of these in 4 patients (CRF [redacted] and [redacted]) the investigator had documented increased use of inotropes during the first 6 hours of ATryn® treatment. For two patients (CRF [redacted] and [redacted]) a decrease of more than 20% in the baseline MAP was recorded.

Adverse events: As would be expected from such very ill patients all study patients experienced adverse events. During the study 127 AEs (that emerged after treatment start) were reported in addition to 57 critical events. Only 15 of the reported adverse events were considered at least possibly related to the study treatment.

In the 150-AT group 7 AEs assessed as possibly related to study drug were reported from 6 patients. In the 250-AT group 8 AEs assessed as possibly related to study drug were reported from 4 patients. No AEs in the control group were considered to be related to standard therapy or study procedures.

From patients treated with ATryn® 3 reports were nervous systems disorders, 3 from general disorders and administration site conditions, 2 from blood and lymphatic system disorders, 2 from vascular system disorders 1 from thoracic and mediastinal disorders and 1 skin and subcutaneous tissue disorders

Safety laboratory evaluation did not indicate any adverse effects of ATryn® on these parameters.

The development of IgM and IgG antibodies to recombinant antithrombin and goat antithrombin and goat milk proteins were evaluated in two separate bioanalytical studies. One patient ([redacted]) developed Anti-rhAT IgM but no IgG antibodies. No patients developed antibodies against goat antithrombin or antibodies against goat milk proteins.

Conclusion:

The present study was not conclusive since it was stopped very prematurely. Obviously the efficacy cannot be

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: ATryn®	Volume:	
Name of Active Substance: (recombinant) antithrombin alfa	Page:	

judged but the trend did not indicate any benefit from the use of ATryn® since the observed number of deaths were higher in the ATryn® treated groups and no positive trends were seen in any of the other efficacy variables.

As could be expected in this patient population all patients suffered from AEs and most from SAEs. There was no suggestion that ATryn® caused more SAEs than standard treatment. The narratives suggest that progression of the underlying multiorgan failure was the usual cause of death. Mortality in the control group was lower than expected.

There was no clear pattern from this patient population indicating any specific side effect profile from ATryn®. Increased bleeding is a known potential side effect but, overall, bleeding did not appear to be more frequent among ATryn® treated patients than in control patients that received standard treatment.

This inconclusive, very small study does not show any evidence of efficacy of ATryn® in this population but there is no evidence of any specific toxic effect.

Date of report:
18-DEC-2009

2.1 SCHEDULE/CHART OF STUDY PROCEDURES (PROTOCOL VERSION 3)

	Pre-treatment	**Treatment**			**Follow-up**		
Day	Baseline – prior to randomisation	1 – post randomisation	2-5	6	7	28 ±5	90 ±7
Informed consent	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]
In-/exclusion criteria	X						
Patient demographics	X						
Pregnancy test[2)]	X						
Medical history	X						
Microbiological culture[3)]	X						
Concomitant diagnoses	X						
Concomitant treatment[4)]	X	X	X	X			
Physical assessment	X[5)]	X	X	X			
Randomisation		X					
Adverse event(s)	X[6)]	X	X	X	X	X[6)]	X[6)]
Critical event(s)		X	X	X	X	X	X
Compression ultrasound	X[7)]			X[7)]			
Chest X-ray/CT scan	X[8)]						
Laboratory – haematology	X[5)]	X[9)]	X[9)]	X[9)]	X[10)]	X[10)]	X[10)]
Laboratory – immunology	X[11)]	X[11)]			X	X	X
Laboratory - inflammation	X[11)]	X[11)]	X	X			
Laboratory – biochemistry	X[5)]	X	X	X			
Blood gases (arterial)	X[5)]	X	X	X			
Vital signs	X[5)]	X	X	X			
Organ support/organ failures	X	X	X	X		X	
Urine output	X	X	X	X			
Evaluation scores (SAPS II, DIC and SOFA) [12)]	X	X	X	X			
Administration of trial medication		X[13)]	X[13)]	X[13)]			
Days on ventilation, days with inotrope/vasopressor support						X	
Date of discharge from ICU and hospital		X	X	X	X	X	X
Quality of life questionnaire						X	X
If applicable: reason and date		X	X	X	X	X	X

of death							

Assessments that are to be performed daily should be performed during the morning. The value obtained closest to 9 am should be reported. The exception to this is day 1 where the assessment should be performed as close to time 23:59 as possible.

1) See protocol section 6.4. At inclusion the patient or the legally acceptable representative will be asked to consent. The patient will be asked to give their own consent whenever possible
2) For women of child-bearing potential a urine or serum pregnancy test must be performed within 24 hours prior to randomisation
3) Should be obtained if not already taken during present sepsis episode. Preferably results obtained prior to anti-microbial therapy should be reported
4) Including transfusion of blood products, IV fluids, prophylactic use of compression stockings/pneumatic compression, and anticoagulant treatment used prior to 6 hours (UFH) or 18 hours (LMWH) preceding randomisation
5) Assessments should be performed within 24 hours prior to randomisation
6) Serious adverse events should be reported from time of signed informed consent. After day 7 only serious adverse events that come to the investigator's knowledge by questioning the patient or from hospital records should be reported.
7) Baseline assessment may have been performed within 24 hours prior to randomisation or may be postponed until day 3 in asymptomatic patients. The final assessment should be performed at day 6 (+24 hours) or at discharge from ICU whichever comes first
8) Only patients included with respiratory infection and/or respiratory failure. This imaging assessment should be performed within 48 hours prior to randomisation.
9) See protocol section 11.7.5.1 and 11.7.5.2 for details on which coagulation/haematology parameters to be analysed at the local and central laboratory respectively.
10) Only antithrombin activity to be analysed at the central laboratory.
11) Central laboratory testing only. May be performed in the time interval; within 24 hours prior to randomisation and 3 hours after randomisation
12) SAPS II only at baseline. SAPS II should be calculated based on data collected during the first 24 hours after ICU admission. For further information on the scores, see Appendix 4.
13) Patients randomised to the ATryn® arms should receive a loading IV dose and subsequent continuous infusion (maintenance dose) for 120 hours from the time of the initial administration of the loading dose.

LEO90010-I21 Clinical Study Report Synopsis EudraTC no. 2006-002873-35 18-Dec-2009 - English

ELECTRONIC SIGNATURES

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
[redacted]	[redacted], International Clinical Development Approval	21-dec-2009 13:32 GMT+01
[redacted]	[redacted] Biostatistics Approval	21-dec-2009 15:44 GMT+01